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AUSTRALASIAN ANNALS OF MEDICINE

Journal of The Royal Australasian College of Physicians

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AUSTRALASIAN ANNALS OF MEDICINE

VOLUME 4 MAY, 1955 NUMBER 2

EOSINOPHILIC GRANULOMATOSIS[1]

JOHN McDONALD AND LORIMER DODS

From the Royal Alexandra Hospital for Children and the Institute of Child Health, Sydney

> The decorous obscurity of the ancient languages is used to conceal an immense diversity of principles . . . terms which lend a kind of formal majesty to our ignorance.
>
> —SIR WALTER RALEIGH "The Origin of Romance"

OUR purpose in submitting this communication is to draw attention to an uncommon disorder of childhood which is characterized by an unexplained eosinophilia of marked degree, enlargement of the liver and occasional enlargement of the spleen. With some hesitation, we have chosen the title of "eosinophilic granulomatosis"—a euphonious label which probably does little more than "lend a kind of formal majesty to our ignorance" about this disorder and its ætiology.

In 1949 this syndrome was clearly defined for the first time by Zuelzer and Apt, who published a detailed clinical review of eight children suffering from "disseminated visceral lesions associated with extreme eosinophilia" and recorded the histological changes in the liver and other organs of four of these children. It is very difficult to assess the number of examples of this disorder which had been reported prior to 1949, as the titles under which probable cases were recorded during this period varied widely and very few pathological studies were reported. One of the earliest case reports was published by Bass in 1925 under the title of "Unusual Eosinophilia with Splenomegaly (Eosinophilic Leukæmia ?)", and during the next twelve years published records of several children who were probably suffering from this disorder appeared under titles varying from "Eosinophilic Leukæmia" to "Chronic" or "Familial Eosinophilia".

The following brief description of the clinical features and the pathological changes of eosinophilic granulomatosis is based, in the main, on the observations recorded by Zuelzer and Apt (1949).

CLINICAL PICTURE

Most of the affected children are aged between eighteen months and three or four years.

A large number of these children are reported to have suffered from asthma, urticaria or some other allergic manifestation.

Significant enlargement of the liver is a very common feature. Our experience and some of the case reports suggest that the spleen may be enlarged; but Zuelzer and Apt express doubt about this, and emphasize the usual hazard of mistaking the enlarged left lobe of the liver for an enlarged spleen.

A considerable degree of eosinophilia is an essential feature. In the reported cases the number of eosinophile cells varies from 1500 to 100,000 per cubic millimetre of blood and may be responsible for raising the total leucocyte count to levels of 100,000 or more per cubic millimetre.

Significant eosinophilia may be noted in other siblings.

PATHOLOGICAL CHANGES

According to Zuelzer and Apt, the essential pathological changes in the liver are widespread eosinophilic infiltrations associated with focal necrosis and granuloma formation, followed by a healing process which takes the form of fibrosis, encapsulation and occasionally calcification.

[1] Received on November 22, 1954.

Zuelzer described areas of sharply circumscribed necrosis which were present in the midst of massive eosinophilic infiltrations, and pointed out that these pathological changes were most pronounced in the portal tracts of the liver, but were sometimes evident to a lesser degree in the spleen and in the mesenteric and mediastinal lymphatic glands.

Beaver and his colleagues (1952) have described the finding of a larval nematode (*Toxocara canis*) in sections of the liver from a child suffering from "eosinophilia with granulomatous lesions of the liver", and as a result have suggested that this syndrome may be a visceral form of *larva migrans* infestation.

Zuelzer states that the marrow appears normal, apart from "a large but orderly increase in the number of eosinophil granulocytes".

PROGNOSIS

It seems that the great majority of the affected children make a satisfactory recovery within a period of six months to four years after the onset of this disorder.

CASE REPORTS

In September, 1949, one of us (L.D.) was consulted about a boy, aged two and a half years, who had been noticed to be pale and tired for a few weeks. His parents, who were both medical practitioners, had recently discovered that his liver extended at least four fingers' breadth below the costal margin and that his spleen was easily palpable. A blood count carried out at this time revealed hypochromic anæmia and a gross increase in the number of leucocytes (more than 50,000 per cubic millimetre), of which 52% were eosinophile cells. At the time of this first consultation, the frightening possibility of eosinophilic leuchæmia was distressing the parents, and later the fact that a paternal aunt was found to be suffering from leuchæmia naturally aggravated this anxiety. The history of this boy's illness was as follows:

CASE I.—M.D., aged two and a half years, had always been well until August 16, 1949, when he suffered an attack of asthma which was relieved by a hypodermic injection of adrenaline. Reports on radiographs of his chest, taken at this time, recorded "increased markings throughout the lung fields suggestive of acute bronchitis" and "a few discrete areas suggesting bronchopneumonia in the right mid-lung zone" which were not obvious in a radiograph taken forty-eight hours later. During the next few weeks his parents noticed that he was pale, that he tired easily and that his abdomen was more protuberant than usual. It was during this period that his parents first discovered that his liver was palpable at least four fingers' breadth below the costal margin and that his spleen was easily palpable. A blood count, carried out at this time, revealed hypochromic anæmia associated with gross leucocytosis (more than 50,000 leucocytes per cubic millimetre) and pronounced eosinophilia (see Table I). At the parents' request, examination of the bone marrow was not performed.

Radiographs of the long bones revealed a narrow band of increased density close to the epiphyseal line which was most pronounced at the upper ends of the humeri and the lower ends of the femora. Dr. H. R. Sear, who examined these radiographs, pointed out that the bands of increased density did not suggest leuchæmia, were similar in some respects to those following excessive administration of vitamin *D*, and were not unlike the changes associated with lead poisoning during childhood. An X-ray examination of the abdomen suggested considerable enlargement of the liver, and some enlargement of the spleen. Examination of his fæces for parasites, the Casoni test and a complement fixation test for hydatid disease all gave negative results.

Within a month the total number of leucocytes had risen to a level of 143,000 per cubic millimetre and the eosinophile cells to a level of 123,152 per cubic millimetre. A number of eosinophile myelocytes were noted on several occasions, but the other leucocytes remained mature and the blood platelets were regarded as plentiful throughout the illness. A month later there was a significant fall in the total leucocyte and eosinophile cell counts, the enlargement of the liver was less obvious and the spleen was not palpable (see Figure I).

Finally, early in April, 1950, about seven months after the onset of the disorder, the leucocyte and eosinophile counts had fallen to normal levels, there was no obvious anæmia, the liver was no longer

TABLE I

Case I: M.D., Aged Two and a Half Years

Date	Hæmoglobin Value Grammes *per Centum*	Erythrocytes per Cubic Millimetre	Leucocytes per Cubic Millimetre	Absolute Numbers of Leucocytes per Cubic Millimetre.				
				Neutrophile Cells	Lymphocytes	Monocytes	Eosinophile Cells	Eosinophile Myelocytes
7.10.49	7·5	3,200,000	50,650	8610	15,195	506	26,338	—
8.10.49	—	—	80,600	3224	8060	806	67,704	806
14.10.49	8·7	3,700,000	50,250	6532	9045	—	34,672	Nil
3.11.49	—	—	92,750	4637	12,047	—	78,047	1850
4.11.49	8·9	2,920,000	143,200	5728	11,456	—	123,152	2864
12.12.49	9·0	3,200,000	61,000	2400	6710	610	51,240	Nil
17. 3.50	11·0	4,280,000	17,600	2464	4400	440	10,208	88
14. 4.50	—	—	12,000	—	—	—	2000	—

TABLE II

Sister of M.D. (Case I), Aged Four and a Half Years

Date	Leucocytes per Cubic Millimetre	Absolute Numbers of Leucocytes per Cubic Millimetre				
		Neutrophile Cells	Lymphocytes	Monocytes	Eosinophile Cells	Immature Forms
8.11.49 ..	7700	2541	3157	231	1771	Nil
12.12.49 ..	12,500	4500	5500	1125	1375	Nil

palpable and the child seemed to be in excellent health.

The patient's sister, aged four and a half years, was found to have an absolute eosinophilia of 1375 to 1770 per cubic millimetre when examined during the second month of her brother's illness (see Table II).

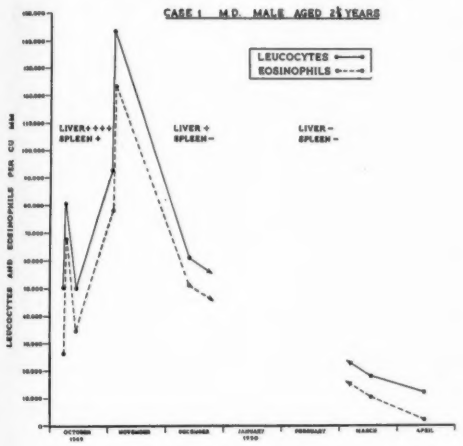


FIGURE I

Case I: M.D., aged two and a half years

The second patient was aged two years and nine months when he first attended the Royal Alexandra Hospital for Children in December, 1952, for the treatment of epilepsy. It was then noted that his spleen was palpable one finger's breadth below the costal margin, and a blood count revealed 5250 eosinophile leucocytes per cubic millimetre out of a total leucocyte count of 15,000 per cubic millimetre. The history of his illness was as follows:

CASE II.—J.R., a male patient, aged two years and nine months, attended the out-patient department of the Royal Alexandra Hospital for Children in December, 1952, because of seizures which had commenced one month previously. He had been in good health prior to this date, and there was no family history of epilepsy or allergy or of any significant illnesses. It was noted that his spleen was palpable one finger's breadth below the costal margin, and a blood count revealed a leucocytosis of 15,000 per cubic millimetre and 5250 eosinophile cells per cubic millimetre (Table III and Figure II). His fundi were normal in appearance, and no clinical abnormality of his nervous system was detected. His electroencephalogram was regarded as normal, and the result of the Wassermann and Kline tests of his blood was negative.

In May, 1952, when the eosinophile cell count had reached 23,310 per cubic millimetre out of a total leucocyte count of 63,000 per cubic millimetre, he was admitted to hospital for further investigation. Repeated examinations of his fæces failed to reveal any parasites, and the results of the Casoni test and a complement fixation test for hydatid disease both proved negative. Radiographs of his long bones revealed a narrow band of increased density extending across the breadth of the metaphysis at its junction with the epiphyseal line in the lower ends of the femora, at both ends of the tibiæ and fibulæ, and at the lower ends of the radii and ulnæ (Figure III). These radiographic changes were

TABLE III

Case II: J.R., Aged Two Years and Nine Months

Date	Hæmoglobin Value (Grammes *per Centum*)	Erythrocytes per Cubic Millimetre	Leucocytes per Cubic Millimetre	Absolute Numbers of Leucocytes per Cubic Millimetre				
				Neutrophile Cells	Lymphocytes	Monocytes	Eosinophile Cells	Basophile Cells
5.12.52	—	—	15,000	4200	5100	450	5250	—
28. 1.53	—	—	15,800	5056	4740	948	5056	—
9. 2.53	—	—	11,700	7203	4410	882	2205	—
10. 3.53	—	—	16,000	4000	4960	—	7040	—
20. 4.53	—	—	63,000	8190	31,500	—	23,310	—
7. 5.53	12·0	4,600,000	14,300	2002	2860	143	9295	—
12. 5.53	11·5	4,510,000	19,400	4268	4268	388	10,476	—
22. 5.53	—	—	19,300	7334	2316	1158	8492	—
13. 7.53	—	—	17,700	11,328	4248	1062	1062	—
9. 9.53	—	—	15,000	4500	4350	450	5550	150
19.10.53	—	—	12,000	4200	1800	120	5880	—
12.12.53	11·5	—	15,000	12,550	1800	—	450	—
23.12.53	11·2	—	10,000	6400	3200	—	400	—
31. 5.54	12·2	4,680,000	13,000	5070	5200	—	2730	—

similar to those found in the long bones of children suffering from lead poisoning. The total protein content of his serum was estimated to be 6·7 grammes *per centum* (serum albumin 4·1 grammes *per centum*, serum globulin 2·6 grammes *per centum*); the results of both the thymol turbidity and thymol flocculation tests were regarded as normal. The erythrocyte sedimentation rate was recorded as five millimetres in one hour (Westergren). The cerebro-spinal fluid was

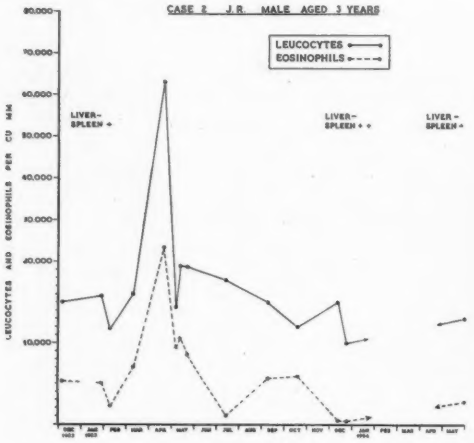


FIGURE II

Case II: J.R., aged two years and nine months

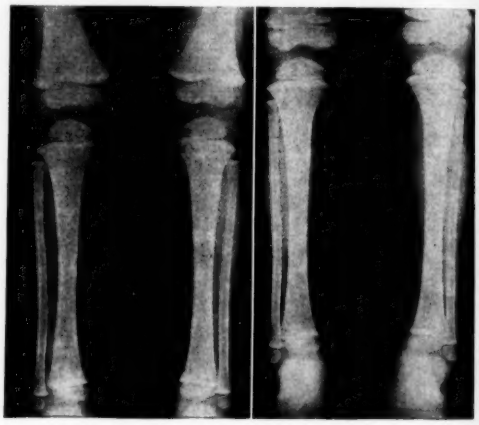
normal in all respects. A twenty-four-hour specimen of urine was found to contain only 0·03 milligramme of lead per litre, and examination of the blood did not suggest a diagnosis of lead poisoning.

Blood counts were performed on the other members of the family, and the two siblings were found to have an increased number of circulating eosinophile cells (Table IV).

In December, 1953, more than twelve months after the onset of the illness, the spleen was palpable two fingers' breadth below the costal margin, the liver was not obviously enlarged, the eosinophile cells numbered only 400 per cubic millimetre and the leucocyte count had fallen to 10,000 per cubic millimetre. At this stage skiagrams of the long bones showed changes similar to those noted earlier in April, 1953 (Figure III). Within the next few months this patient suffered from a prolonged series of major seizures, which were eventually controlled by anti-convulsant drugs. During this period an electroencephalogram revealed the changes usually associated with *status epilepticus*.

When he was reexamined in June, 1954, he was still subject to frequent attacks of epilepsy, the spleen was palpable one finger's breadth below the costal margin, the eosinophilia was again apparent (2730 eosinophile cells per cubic millimetre of blood), and skiagrams of the long bones revealed obvious narrowing of the bands of increased density which had been noted a year earlier (Figure III).

In May, 1953, while the second patient (Case II) was still in hospital, a third child, aged twenty-three months (Case III) was admitted to the hospital suffering from lead encephalopathy, and was found to have a total leucocyte count of 160,000 per cubic millimetre,



April, 1953 June, 1954

FIGURE III

Narrow bands of increased density extending across the breadth of the metaphyses at their junctions with the epiphyseal lines

of which 123,000 per cubic millimetre were eosinophile cells. The liver, spleen and cervical and inguinal lymph nodes were all enlarged at the time of his admission to hospital.

CASE III.—One morning in May, 1953, a boy in convulsions, B.H., aged twenty-three months, was admitted to the Royal Alexandra Hospital for Children.

TABLE IV

Leucocyte Counts of Parents and Siblings of J.R. (Case II)

Subject	Leucocytes per Cubic Millimetre	Absolute Numbers of Leucocytes per Cubic Millimetre				
		Neutrophile Cells	Lymphocytes	Monocytes	Eosinophile Cells	Basophile Cells
Father ..	7400	3700	2738	518	444	—
Mother ..	7000	4200	2100	420	280	—
Brother ..	9000	4500	2700	720	990	90
Sister ..	11,000	5280	4400	220	1100	—

His parents stated that he had been in good health until a few months previously, when he became irritable and lost his appetite. On further questioning, the parents admitted that this child was an avid "dirt eater", and that old paint was peeling off the garden fence

Radiographs of the long bones showed the changes associated with lead poisoning (Figure V). A blood count revealed many "stippled cells" and reticulocytes (160,000 per cubic millimetre) represented 4% of the erythrocytes which totalled 4,000,000 per cubic millimetre. The protein content of the cerebro-spinal fluid was found to be 110 milligrammes per 100 millilitres on the day of the boy's admission to hospital, and ten days later had fallen to 30 milligrammes per 100 millilitres. No other chemical abnormality was detected in the cerebro-spinal fluid, and there was no pleocytosis. Confirmation of the diagnosis of lead poisoning was complete when a twenty-four-hours specimen of urine was found to have a lead content of 1·0 milligramme per litre. In addition, the paint flakes from the garden fence were found to have a high lead content.

Although there was no doubt that this child was suffering from lead poisoning, the final diagnosis was still in doubt, as the liver was enlarged three fingers' breadth below the costal margin, the spleen was palpable, there was a moderate degree of enlargement of the cervical and inguinal lymph glands, and a pronounced absolute eosinophilia was present. The initial blood count had demonstrated the characteristic changes of lead poisoning, but in addition there was a gross leucocytosis of 160,000 per cubic millimetre, of

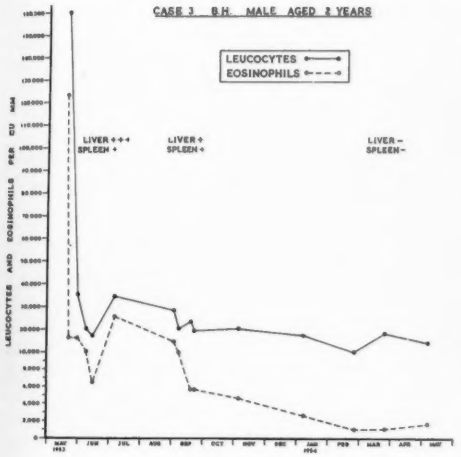
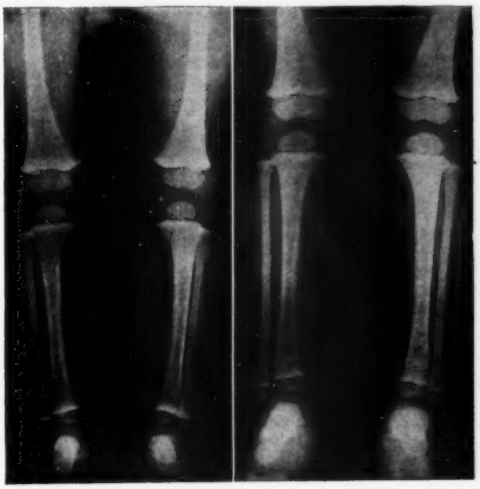


FIGURE IV

Case III: B.H., aged twenty-three months



May, 1953 May, 1954

FIGURE V

Narrow bands of increased density extending across the breadth of the metaphyses at their junctions with the epiphyseal lines

TABLE V

Case III: B.H., Aged Twenty-three Months

Date	Hæmoglobin Value (Grammes *per Centum*)	Erythrocytes per Cubic Millimetre	Leucocytes per Cubic Millimetre	Absolute Numbers of Leucocytes per Cubic Millimetre					
				Neutrophile Cells	Lymphocytes	Monocytes	Eosinophile Cells	Basophile Cells	Immature Leucocytes
20.5.53 ..	10·0	4,000,000	160,000	16,000	16,000	1000	123,000	—	3200
22.5.53 ..	—	—	37,000	8510	9990	1480	16,280	—	740
26.5.53 ..	8·5	4,000,000	35,000	10,500	6300	350	16,100	—	1750
9.6.53 ..	6·8	3,380,000	20,000	2800	5000	2200	10,000	—	—
15.6.53 ..	9·5	4,000,000	17,000	4760	4760	680	6460	340	—
25.6.53 ..	9·0	—	—	—	—	—	—	—	—
6.7.53 ..	10·2	4,700,000	34,000	2380	5440	680	25,500	—	—
3.9.53 ..	11·2	3,660,000	28,000	5600	7280	1120	14,000	—	—
7.9.53 ..	11·0	4,090,000	20,000	2600	5600	2000	9900	—	—
19.9.53 ..	12·0	—	23,000	6900	9200	1380	5520	—	—
22.9.53 ..	11·0	4,540,000	19,000	2850	9880	380	5510	380	—
5.11.53 ..	12·2	—	20,000	4000	9800	1600	4400	—	200
7.1.54 ..	11·8	4,230,000	17,000	5610	8330	510	2550	—	—
26.2.54 ..	12·3	4,300,000	10,000	2600	5400	900	1000	100	—
25.3.54 ..	14·0	4,800,000	18,000	9720	4860	2160	1080	180	—
6.5.54 ..	13·9	4,570,000	14,000	3640	8260	560	1540	—	—

TABLE VI
Leucocyte Counts of Three Siblings of B.H. (Case III)

Subject	Leucocytes per Cubic Millimetre	Absolute Numbers of Leucocytes per Cubic Millimetre				
		Neutrophile Cells	Lymphocytes	Monocytes	Eosinophile Cells	Basophile Cells
Brother (twelve years) ..	12,000	7320	3240	600	840	—
Brother (nine years) ..	10,000	5700	3300	400	400	200
Brother (four years) ..	14,000	6300	5460	420	1820	—

which 123,000 cells per cubic millimetre were eosinophiles. Two days later the total number of leucocytes had fallen to 37,000 per cubic millimetre, of which 16,280 were eosinophile cells (Table V and Figure IV). The total protein content of the serum was estimated to be 10·2 grammes *per centum*, the serum albumin content 2·5 grammes *per centum* and the serum globulin content 7·6 grammes *per centum*. An increased erythrocyte sedimentation rate of 23 millimetres in one hour (micro method) was also noted. Bone marrow examination revealed a great increase in the eosinophile elements but the marrow pattern was otherwise normal. Repeated examination of the fæces for parasites and ova, the Casoni test, and a complement fixation test for hydatid disease all gave negative results. Thymol turbidity and flocculation of the serum were normal. An electroencephalogram revealed a four to six cycle per second basic rhythm, with suppression of activity in the right parietal area.

The patient responded well to treatment for the lead poisoning, and the liver decreased in size; but the enlargement of the spleen and lymph nodes remained apparently unaltered during his stay of two and a half months in the hospital. Finally, after a period of about twelve months, the liver, spleen and lymph nodes returned to their normal size. The leucocytosis and the eosinophila persisted (Table V and Figure IV), but did not again reach the high levels recorded at the time of this child's admission to hospital.

Dr. H. R. Sear reported that radiographic examination of the long bones revealed a zone of increased density extending across the breadth of the metaphysis at its junction with the epiphyseal line in the lower ends of the femora, and at the upper and lower ends of the tibiæ and fibulæ. Similar lines were noted in the lower ends of the radii and ulnæ and were also present, though not so pronounced, in the lower ends of the humeri, in the upper ends of the radii and in the metacarpals (Figure V). Dr. Sear reported that these changes in the radiographic appearance of the long bones were identical with those found in association with lead poisoning.

Blood counts of the other members of the family revealed a minor degree of eosinophilia in two of the three siblings (Table VI). These two children were found to have a slightly increased amount of lead in their urine, but did not present any other evidence of lead poisoning and were apparently well. Repeated examination of these children failed to reveal any obvious enlargement of the liver, spleen or superficial lymph glands.

A second bone marrow examination carried out in September, 1953, about four months after the previous one, revealed no significant changes apart from a pronounced increase in the eosinophile elements.

When this patient was last examined, in May, 1954, he appeared to be in normal health, his liver, spleen and superficial lymph nodes were not enlarged, and the globulin content of his serum had returned to a normal figure (2·8 grammes *per centum*). Further skiagrams of the long bones confirmed the presence of the bands of increased density close to the epiphyseal lines in the metaphyses; but these were less pronounced, and narrower than those noted in the previous X-ray films (Figure V).

DISCUSSION

Association with Other Diseases

The association of this syndrome of eosinophilia, hepatomegaly and splenomegaly with asthma and radiographic evidence of transient "infiltrations" of the lungs has been recorded by several observers. One child observed by us (Case I) suffered from an attack of asthma, associated with radiographic evidence suggesting transient pulmonary "infiltrations", which occurred at the beginning of his six months' illness.

The incidence of seizures amongst affected children appears to be surprisingly high. Zuelzer and Apt reported that four of their eight patients suffered from convulsions, and two of our three patients were originally brought to physicians because of seizures. One child (Case II) was subject to frequent seizures throughout his illness; this tendency has persisted, and his electroencephalogram supports a diagnosis of epilepsy. The other child (Case III) was originally admitted to hospital during a convulsive seizure which was assumed to be the result of an associated lead encephalopathy.

Blood Changes

Zuelzer and Apt have directed attention to the very high degree of leucocytosis which is a notable feature of this disease, and have quoted counts as high as 117,000 leucocytes per cubic millimetre of blood. In our three patients the leucocytosis was very pronounced, and in one of these children (Case III) reached a level of 160,000 leucocytes per cubic millimetre of blood. This great increase in the total number of leucocytes in the peripheral blood was due, in the main, to the gross eosinophilia; but on

various occasions there was also a significant increase in the neutrophile cells, the lymphocytes and the monocytes. A variable degree of unexplained anæmia has been described by other observers as an occasional feature of this disorder and was noted in one child (Case I) during the early months of his illness.

Bone Marrow

Zuelzer and Apt examined the bone marrow of five of their patients, and noted that the pattern was normal apart from "a large but orderly increase in the number of eosinophil granulocytes". The bone marrow of one of our patients was examined twice, and on each occasion no abnormality was detected apart from a considerable increase in the number of eosinophile granulocytes.

Eosinophilia in Siblings

Various observers have emphasized the frequent association of this disorder with eosinophilia in other members of the family. With one exception, all the siblings of our three patients were found to have eosinophilia. These siblings apparently enjoyed normal health and did not exhibit any evidence of enlargement of the liver or spleen.

Enlargement of the Liver and Spleen

Zuelzer and Apt have emphasized enlargement of the liver as a very common feature of this disorder, but have expressed doubt about an associated enlargement of the spleen. In two of our patients (Cases I and II) the liver was obviously enlarged and progressively decreased in size until at the conclusion of the illness it appeared to have reached its normal size. Clinical examination suggested that the spleen was enlarged in all three of our patients, and this apparent enlargement of the spleen subsided simultaneously with the return of the liver to normal size.

The pathological changes in the liver reported by Zuelzer and Apt as characteristic of so-called "eosinophilic granulomatosis" have been described above. In view of the fact that the clinical and pathological evidence strongly suggested that the three children reported by us were all suffering from this disease, liver biopsy was not regarded as an essential procedure and was therefore not performed.

Radiographic Changes in the Long Bones

We have been unable to find any references in the literature to associated radiographic changes in the long bones, except for one patient reported by Zuelzer and Apt as suffering from lead poisoning whose skiagrams revealed characteristic "lead lines", and one other patient of their series whose X-ray films suggested some thickening of the cortex in the proximal and middle portions of both ulnar bones.

In all three cases of our series, radiographic examination of the long bones revealed well marked, narrow zones of increased density extending across the breadth of the metaphysis at its junction with the epiphyseal line (Figures III and V). These radiographic changes were similar in many respects to those found in the long bones of children suffering from lead poisoning, and one of our patients (Case III) was proved to be suffering from this condition. The remaining two children did not present any other evidence of lead poisoning, and it seemed reasonable to assume that the radiographic changes in their long bones were probably not those of plumbism, although this possibility cannot be denied. Progress skiagrams of the long bones of two of our patients, taken approximately one year after the onset of the disorder, still showed these bands of increased density, which were, however, narrower and less obvious at this stage.

Differentiation from Leuchæmia

The differentiation of this relatively benign disease from the extremely rare condition of eosinophilic leuchæmia is obviously of great importance.

Ætiology.—The frequent association of this syndrome with clinical signs of allergy, such as asthma and urticaria, suggests that the eosinophilia and the associated visceral lesions may be manifestations of a "tissue hypersensitivity". Although most observers, including Zuelzer and Apt, have failed to find any evidence of helminthiasis or of other intestinal parasites, Beaver and his colleagues observed a larval form of *Toxocara canis* in the sections of the liver from one of their patients. Beaver has argued that the syndrome under discussion may be explained on the basis of direct tissue damage by the migrating larvæ of *T. canis* and an associated allergic response to their products. Apparently these larvæ may survive for relatively long periods in the liver and may be responsible for the production of granulomatous lesions and associated eosinophilic infiltrations. This theory of visceral infestation by migrating larvæ seems to offer a reasonably satisfactory explanation of this syndrome, but should not be accepted without further supporting evidence. At present, the demonstration of larvæ in the liver or possibly

in other viscera represents the only satisfactory method of establishing their presence.

" Pica " or " dirt eating " as a method of ingesting ova, parasites or other noxious substances including lead, is a habit which belongs particularly to the period of infancy during which eosinophilic granulomatosis usually occurs. It seems possible that this infantile practice may explain the association of lead poisoning and of eosinophilic granulomatosis, as recorded in one of Zuelzer's reported cases and in one of our cases.

SUMMARY

The clinical and hæmatological characteristics of an uncommon and relatively benign disorder of early childhood have been reviewed. The outstanding features of this disorder include pronounced leucocytosis, gross eosinophilia, enlargement of the liver and occasional enlargement of the spleen. These manifestations usually subside within a period of about eighteen months or less, but may persist for three or four years or even longer. The affected children are usually aged between eighteen months and four years.

The cases of three children who were apparently suffering from this disorder have been reported. The ages of these children varied from twenty-three to thirty-one months, and the disorder apparently subsided within a period of seven to eighteen months after its first recognition. Two of the three children were subject to recurrent seizures, and one of these children was found to be suffering from lead poisoning.

Radiographs of the long bones of the child suffering from lead poisoning showed the classical " lead lines " associated with plumbism. Radiographic examination of the long bones of the other two children also revealed narrow bands of increased density extending across the breadth of the metaphysis at its junction with the epiphyseal line ; these bands were similar in many respects to those noted in children suffering from lead poisoning. These changes in the radiographic appearances of the long bones of children suffering from " eosinophilic granulomatosis " have not been described by other observers, and their explanation remains obscure.

Five of the six siblings of the three children reported were found to have eosinophilia.

The ætiology of " eosinophilic granulomatosis " has not been established, but the possibility of direct tissue damage by the migrating larvæ of *T. canis* has been suggested, and this concept of " visceral *larva migrans* " seems to offer a reasonable explanation of the major features of this order.

It is suggested that " pica " or " dirt eating " as a method of ingesting parasites, ova and substances containing lead during infancy may possibly explain the occasional association of this syndrome with lead poisoning.

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THE INVESTIGATION OF FEVERS IN NORTH QUEENSLAND BY MOUSE INOCULATION, WITH PARTICULAR REFERENCE TO SCRUB TYPHUS[1]

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In 1951, an investigation of the fevers of North Queensland was begun by the Queensland Institute of Medical Research, acting particularly through a field station established at Innisfail. Cases of leptospirosis, scrub typhus, "Q" fever and other infections were recognized, but there remained a considerable residue of cases that defied diagnosis by the usual laboratory methods and were perforce labelled "Pyrexia of Unknown Origin" or "P.U.O.". In an attempt to elucidate their nature, a programme of mouse inoculation was carried out.

In November, 1951, mice had been successfully inoculated with blood from a scrub typhus patient by Dr. C. N. Sinnamon, then senior research fellow attached to the field station. Some inoculations were made in October, 1952, and from March, 1953, they were carried out regularly. Up till April, 1954, a total of 131 cases of fever had been investigated in this way.

The mice of the Institute stock are large and multicoloured, and were derived in 1949 from the Walter and Eliza Hall Institute of Medical Research, Melbourne.

Blood was taken from the patient during the febrile period, as early in the illness as possible, and preferably before specific therapy was instituted. A standard technique was developed, by which two mice were inoculated with clot ground up with alundum in physiological saline, each receiving one millilitre intraperitoneally and 0·03 millilitre intracerebrally. The inoculations were performed at the field station at Innisfail. During 1953 the mice were dispatched to Brisbane two to four days after inoculation, and were observed and passaged there. From December, 1953, and in a few earlier instances, the mice were observed at Innisfail, passaged, and sent to Brisbane only after signs of infection were found. Thus all infective agents obtained in the mice eventually came to Brisbane for further study. If the inoculated mice showed no signs of infection, a number of blind passages, at least two and in most cases four, were made before the case was discarded as "negative". There were minor variations in technique in some of the earlier cases; thus four sets of mice were inoculated with citrated blood, and in 36 intraperitoneal inoculation only was performed.

It had been reported in 1952 by Dr. Sinnamon that among the cases of "P.U.O." were a group which resembled scrub typhus in locality of origin, clinical course and response to chloramphenicol, but in which no agglutinins for *Proteus* OXK were found in the serum. In selecting cases for mouse inoculation, this group was kept especially in mind, and all available cases in which the history suggested scrub typhus were included. On the other hand, clinically typical cases of leptospirosis were excluded. In many cases the diagnosis was indefinite at the time when the mouse inoculation was made.

Results of Mouse Inoculation

Rickettsia Tsutsugamushi

The outstanding result of the inoculations was the isolation of 31 strains of *Rickettsia tsutsugamushi*. We have formed the impression that mouse inoculation is an extremely reliable diagnostic method for scrub typhus. The mice proved to be highly susceptible, and in only one case known to be scrub typhus did mouse inoculation fail. In this case the blood for inoculation was taken on the sixteenth day of illness, and only one blind passage was made. In three cases inoculation was successful, although the blood sample had been four days in transit.

Information about the patients from whom the strains were obtained is summarized in Table I.

[1] Received on October 26, 1954.

TABLE I

Scrub Typhus Patients from whom R. tsutsugamushi was Isolated

Patient	Sex	Age (Years)	Locality, Occupation	Date of Onset	Eschar	*Proteus* OXK Agglutination	
						Day of Illness	Reciprocal Titre
UGA	M.	32	Silkwood, canefarmer	28.10.51	NR[1]	12	0[2]
						34	640
						67	160
MIL	M.	10	Mossman, scholar	9.10.52	NR	5	0
						24	40
WON	M.	19	Mourilyan, canefarm labourer	8.10.52	NR	9	20
						30	80
						65	0
GAR	M.	39	Bramston Beach, timber cutter	13.10.52[3]	+	9[3]	40
						29[3]	160
						68	20
WER	M.	25	Mourilyan, scrub feller	2. 4.53	NR	3	0
						19	160
WAR	F.	48	Bramston Beach, railway station mistress	27. 4.53	+	3	20
						30	320
						64	0
FAL	F.	18	Meerawa, housemaid	5. 5.53	NR	7	20
						28	640
WIE	F.	35	Daintree, housewife	9. 5.53	+	9	0
						33	80
HUG	M.	21	Bramston Beach, carpenter	19. 5.53	+	6	0
						23	0
						40	0
						117	0
						194	0
FEL	M.	27	Bramston Beach, mechanic	21. 5.53	NR	6	0
						25	0
						76	0
						159	0
CHO	M.	27	Yarrabah, storeman	15.5.53	+	12	0
						29	0
						50	20
						134	0
SOL	M.	28	Harvey's Creek, canecutter	20. 6.53	+	3	0
						29	80
HAM	M.	37	Bingil Bay, timber cutter	20. 6.53	+	10	0
						16	0
						27	0
						46	0
						129	0
DON	M.	5	Mission Beach, scholar	21. 6.53	NR	9	40
						30	20
PAS	F.	26	Mossman, nurse	9. 7.53	NR	9	40
						30	40
						65	0
STA	M.	29	Yarrabah, carpenter	16. 7.53[3]	NR	10[3]	0
						26[3]	0
						44[3]	0
						93[3]	0
POW	M.	32	Yarrabah, labourer	13. 7.53	NR	17	640
						44	320
						72	0
PAV	F.	20	Yorkey's Knob, nurse	22. 7.53	NR	8	0
						38	640
						84	0
MAL	M.	20	Yarrabah, labourer	3. 9.53	NR	7	0
						16	0
						44	0
SEI	M.	57	Mt. Poverty, tin miner	28. 8.53[3]	NR	13[3]	32
						40[3]	32
COL	M.	45	Waugh's Pocket, canefarmer	16.10.53	+	11	256
						26	32
MAG	F.	38	Mt. Sophia, housewife	27.10.53	NR	5	0
						35	0
						150	0
MIN	F.	38	Deeral, housewife	19. 1.54	NR	7	0
						31	0
						49	128
MOL	M.	33	Meerawa, canefarm labourer	29. 1.54	NR	5	0
						20	0
						85	0
VAS	M.	33	Mossman, canefarm labourer	6. 3.54	NR	5	0
						26	128
OBR	M.	62	Mission Beach, farm labourer	6. 3.54	+	5	0
						27	256
MACK	M.	17	Tully, farm labourer	11. 3.54	NR	3	0
						17	32
CRA	M.	29	Abergowrie, canefarmer	23. 2.54	+	14	32
						93	32
SOR	M.	43	Abergowrie, timber getter	26. 2.54	+	11	0
						90	0
BRI	M.	20	Mission Beach, scrub clearer	3. 4.54	+	7	0
						21	128
BLA	M.	63	Mission Beach, timber getter	25. 4.54[3]	+	4[3]	256
						19[3]	256

[1] NR, not recorded. [2] Approximate. [3] "0" denotes <20.

The day of the patient's primary illness on which blood was found infective for mice varied from the third to as late as the seventeenth. A rickettsiæmia therefore prevails throughout the febrile period of scrub typhus. (The day of onset was regarded as the first day on which a definite symptom was present. When the illness came on very gradually, a day of onset was difficult to define.) The blood from patient COL which infected mice was actually taken after the fever was over—on the morning of the first afebrile day.

In some cases investigated late in the fever, the infective blood contained also serum agglutinins for *Proteus* OXK, the titres reaching 1 : 256 and 1 : 640.

With patient HAM, the blood was found infective on the sixteenth day of illness during a relapse, as well as earlier, on the tenth day. This patient had responded promptly to chloramphenicol, treatment with which was begun with one gramme on the evening of the ninth day and continued with 0·5 gramme four-hourly until the thirteenth. The first sample of blood was taken about fifteen hours after therapy had begun. The relapse began on the evening of the fifteenth day. With patient MOL also, blood was found infective during a relapse; its infectivity had not been tested during the primary illness.

Smadel, Traub *et alii* (1949) obtained positive results on mouse inoculation during a first relapse of scrub typhus in 11 of 13 cases, and in one of two cases during a second relapse. These patients were volunteers in an epidemiological experiment and were treated with chloramphenicol quite early in their illness.

Coxiella Burneti

Coxiella burneti was obtained from five patients by mouse inoculation. The blood from one of these patients had been two days in the post and stored for sixteen days at −15° C. before inoculation. There was no mortality among the mice, but if they were examined seven to fourteen days after inoculation, the spleen was found to be enlarged. Giemsa-stained smears of the spleen often showed the characteristically grouped rickettsiæ. The diagnosis was confirmed in all cases at the Laboratory of Microbiology and Pathology, Brisbane, by examination of serum both from the patients and from either mice or sub-inoculated guinea-pigs. In mice, the rickettsial agglutination test on serum taken about twenty-eight days after inoculation proved satisfactory and convenient, titres of 1 : 32 or more being consistently obtained to *C. burneti*. The test nearly always gave positive results at twenty-one days. Complement-fixing antibodies were less frequently demonstrable in our mice and then in lower titre.

Leptospirosis

Among the patients were 26 who were later shown by cultural means or agglutination tests to be suffering from leptospirosis. With two of these, the infecting serotype being *Leptospira australis A*, the inoculated mice developed signs like those in an infected guinea-pig—epistaxis, hæmorrhages in the lungs, congestion of subcutaneous tissue, severe toxic changes in the liver and kidney and jaundice. Some of the passage mice died. Leptospiræ were demonstrated in the kidneys of survivors ten months afterwards.

With a patient infected with *L. australis B*, the mice developed an inapparent infection; there was no sign of illness or of abnormalities *post mortem*, but guinea-pigs inoculated from the mouse organs displayed the lesions of severe leptospirosis. Mice inoculated in passage from another *australis B* patient became symptomless carriers; leptospiræ were seen by dark-ground examination in the kidneys and grown on culture therefrom.

It is likely that some other leptospiral infections would have been found in the mice if the investigations on them had been carried through; these were often discontinued when a report came to hand that a definite diagnosis had been made by culture or agglutination.

A transmissible splenomegaly appeared in the mice inoculated with the blood of one leptospirosis patient. The inoculum probably contained no leptospiræ—at least none grew in culture—and the agent causing the splenomegaly has not yet been identified. However, there is evidence that it may have been derived from the mice.

No infective agent was obtained from the blood of the other 68 patients in this series. They suffered from a variety of febrile conditions. With many, a diagnosis was eventually made—influenza, pneumonia, hepatitis, pleurodynia, typhoid, measles *et cetera*. Others retained the diagnosis " P.U.O." (The isolation of Coxsackie and influenza viruses from fæces and throat washings will be reported separately.)

No neurotropic infective agent was obtained from the series of intracerebral inoculations. In several cases mice inoculated intracerebrally with passage material from a patient with scrub typhus showed systemic evidence of infection without neurological signs.

SCRUB TYPHUS IN MICE

There was considerable variation in the severity of the disease produced in mice by the different North Queensland strains of scrub typhus. This agrees with an observation of Irons (1946) in New Guinea. The most virulent of our strains invariably killed mice in nine to twelve days; there were striking post-mortem signs similar to those described by Dinger (1933) and later workers, and rickettsiæ characteristic of *R. tsutsugamushi* were demonstrable in peritoneal smears. On the other hand, some strains were very mild; the mortality was nil, signs were few and rickettsiæ might not be demonstrable. The recognition of these as scrub typhus infections required the performance of an immunity test.

Of the 31 strains, 13 were classed as virulent; the mortality was or approached 100% within about six passages. Fourteen were mild, the mortality being nil or up to 10%. The remaining four were intermediate in virulence.

The MIL strain is an example of the virulent group. It was isolated in October, 1952, and for twenty-two months has been passaged at intervals of seven to thirteen days by intraperitoneal inoculation of liver-spleen emulsion. Infected mice show signs of illness six to seven days after infection. There are noticeable loss of glossiness, ruffing of fur and decrease of activity. The amount of food and water consumed is greatly reduced. The abdomen is distended, the flanks are sunken, the back is hunched, the eyes are watery and either sunken or almost closed. There is little or no weight gain over the weight at the time of infection. Death occurs from seven days onwards, and the mortality rate among mice not used for passage is 91%.

At autopsy, mice of this strain show pathological changes which are typical of the virulent strains of scrub typhus, with only slight variations in severity from one passage to another. Subcutaneous inflammation is pronounced, and inflammation involves the axillary and inguinal lymph glands and the muscles of the limbs. Occasionally there is a gelatinous exudate adhering to the outer surface of the abdominal musculature, extending to the inguinal regions, where this substance lies in a thick mass. The amount of peritoneal fluid varies, from barely enough to moisten the cavity to upwards of five millilitres. This fluid is thick, fibrinous and cloudy, sometimes tinted with blood. The fluid which almost fills the pleural cavity is watery and contains comparatively few cells.

The heart and lungs are normal in appearance, with few exceptions in which there is some congestion. The liver is pale, and covered with thick fibrinous exudate. The lobes of the liver adhere to each other, and adhesions to stomach, spleen and intestines are common. Splenomegaly is seen in only 35% of mice, and its degree is slight. (In this paper, splenomegaly indicates a splenic index of more than 100. The index is the product of length and breadth in millimetres.) The omentum and peritoneal fat deposits are pink and reduced in size. The kidneys are normal. There is inflammation of the intestines, and diarrhœa is noticed when this inflammation is severe.

Intracellular rickettsiæ are easily demonstrated in smears of the peritoneal fluid, when stained by Giemsa's method. The rickettsiæ occur in large masses within the cytoplasm of large mesothelial cells. These large cells, derived from the peritoneum, have oval nuclei and abundant, clear, light-blue cytoplasm, and stand out conspicuously from the other cells in the smear—lymphocytes, monocytes and polymorphonuclear cells. Only on the rupture or breakdown of the cell wall are the organisms liberated into the fluid.

The GAR strain is in complete contrast to the virulent strains. The mice show no signs of illness; they gain weight and remain active. There is only an occasional death, due to non-specific causes.

At autopsy, mice appear normal in almost every way. The exceptions are the occasional presence of some peritoneal fluid, and the enlargement of the spleen to about twice normal size. Rickettsiæ cannot be demonstrated, even after regular fourteen-day passages for twenty months.

The UGA strain was passaged in mice 47 times in two years, with no increase in virulence. The mortality was nil throughout and splenomegaly, the only sign at autopsy, occurred in 57% of 118 mice. In mice sacrificed at intervals, the spleen was found to reach its maximum size in the third week after inoculation and to return to normal at about four weeks.

An unsuccessful attempt was made to enhance the severity of infection with UGA by adding urethane to the drinking water at a concentration of 0·1%. This treatment was maintained for nine passages. Splenomegaly was reduced to 15 out of 40, compared to 26 out of 40 for the control series drinking tap water without addition.

Suckling mice were used in another attempt, also unsuccessful, to increase the susceptibility to infection with UGA. Five newly-born

litters were inoculated intraperitoneally over three passages and examined from fourteen to twenty-six days afterwards. Only four of 28 mice showed splenomegaly and the series was discontinued.

The WAR strain is interesting because of a gradual increase in virulence. The first mice were inoculated in April, 1953, and the mortality for the first twelve passages was 10 out of 36, at an average time of 14·3 days. Splenomegaly was present in 35 out of 44 of the mice.

From the 22nd to the 34th passages the mortality rate was 100%, and mice became moribund in eight to thirteen days. Splenomegaly became less pronounced, and was present in 15 out of 37. Rickettsiæ were demonstrated in peritoneal fluid of mice of the 25th passage.

In Table II the various manifestations induced in mice by some representative strains are summarized for comparison. There was usually an inverse relationship between mortality and splenomegaly; enlargement of the spleen—the cardinal sign of infection with mild strains—was less evident with virulent strains. Peritoneal fluid was uncommon with mild strains.

Correlation with Clinical Features

The strains in Table II were selected also to illustrate the fact that either mild or virulent strains could cause human infection that was associated with the absence of serum agglutinins for *Proteus* OXK or their presence in low or high titre. This is further discussed below.

In an attempt to make a comparison between virulence in mice and in man, it was observed that the mean period of illness before admission to hospital was significantly shorter for patients infected with virulent strains (4·8±1·81 days) than for those infected with mild strains (7·2±2·19 days). Clinical estimates of severity while the patient was in hospital were as a rule impracticable because of the prompt response to specific treatment. With patient WER, however, the initial clinical course was extremely severe. On the evening of his admission to hospital (on the third day of illness), he had a rigor, followed by a convulsive seizure; the temperature rose to 107·8° F. He vomited copiously, was confused and was sedated with difficulty. He eventually made a good recovery. In mice, the WER strain was virulent.

No human illness in this series was fatal.

Eschars were reported in a larger proportion of patients infected with virulent than with mild strains (Table III), but the difference is not significant.

Virulence was also studied in reference to locality of origin (Table III). From each main endemic centre came strains that differed in their degree of virulence. Thus the Mission Beach-Bingil Bay area was represented by one mild, one intermediate and four virulent strains, Yarrabah by one mild and three virulent strains, and Bramston Beach by three mild strains and one (WAR) which was intermediate on isolation but became virulent on passage.

Passage into Guinea-Pigs

The first four strains isolated in mice were later inoculated into guinea-pigs. MIL strain was carried through seven passages. The only effects, seen in occasional guinea-pigs, were slight fever for one day, enlargement of the spleen and peritoneal fluid. Mice inoculated from the third and sixth passages developed typical signs of fatal scrub typhus. UGA guinea-pigs remained afebrile; occasional splenomegaly and reinfection of mice showed

TABLE II

Representative Results of Mouse Inoculations

Reciprocal Titre of *Proteus* OXK Agglutination in Patient	Strain	Mortality[1]		Splenomegaly[2]		Demonstration of Rickettsiæ	Presence of Peritoneal Fluid	Classification
		Number	Percentage	Number	Percentage			
Less than 20	HUG	2/62	3	40/51	78	–	–	Mild
	HAM	27/52	52	14/34	41	+	+	Intermediate
	STA	25/25	100	13/46	28	+	+	Virulent
40	DON	0/24	0	31/56	55	–	–	Mild
	MIL	48/53	91	23/65	35	+	+	Virulent
160	GAR	3/122	2	46/52	88	–	Occasional	Mild
	WER	32/38	84	8/26	31	+	+	Virulent
640	UGA	0/75	0	67/118	57	–	–	Mild
	FAL	21/45	47	14/18	78	+	+	Intermediate
	POW	24/24	100	19/32	59	+	+	Virulent

[1] Mortality in mice not killed for passage.
[2] Number of mice showing splenomegaly when killed for passage.

TABLE III

Comparative Analysis of Strains according to Locality of Origin, Presence of Eschar, Weil-Felix Reaction in Man and Virulence for Mice[1]

Locality of Origin: Presence or Absence of Eschar	Virulence for Mice			Reciprocal Titre of *Proteus* OXK Agglutination			Totals
	High	Intermediate	Mild	80 or Over	40 to 20	Less than 20	
Cook Shire	—	—	1	—	1	—	1
Douglas Shire	2	—	2	2	2	—	4
Mulgrave Shire:							
Yarrabah	3	—	1	1	1	2	4
Bramston Beach ..	—	1	3	2	—	2	4
Rest of Shire	2	1	4	5	—	2	7
Johnston Shire:							
Mission Beach *et cetera*	4[2]	1	1	3[2]	2	1	6[2]
Rest of Shire	1	0	2	3	—	—	3
Hinchinbrook Shire ..	1	1	—	—	1	1	2
Eschar	6	3	4	8	2	3	13
Eschar not reported ..	7	1	10	8	5	5	18
Totals	13	4	14	16	7	8	31

[1] The figures represent numbers of cases.
[2] One strain originated in that part of Mission Beach which lies in Cardwell Shire.

that the strain had been maintained. The GAR strain could also be maintained for seven passages, but there was neither fever nor splenomegaly. Two attempts to passage WON strain in guinea-pigs were both unsuccessful.

Passage into Yolk Sac

Several strains were adapted to yolk sac passage by Mrs. V. M. Macdonald. When the mild GAR strain, after several passages in yolk sacs, was returned to mice, it was found to be virulent, and the virulence has been sustained in subsequent mouse passage. The enhancement of virulence of GAR for mice after a sojourn in eggs was verified by a repetition of the experiment.

Immunity Tests

Immunity tests were carried out in order to check the relationships of the strains and to establish or confirm their identity as scrub typhus. To this end the two strains MIL and GAR were used. Virulent strains were tested by being used to challenge mice convalescent from the mild infection induced by GAR. Mild or intermediate strains were tested by the challenging of convalescent mice with the virulent MIL strain. Challenges were made at least six weeks after the primary inoculation, the usual inoculum being 0·5 millilitre of a liver-spleen emulsion. Twelve mice and 12 controls were used as a rule for each test, and the mortality was observed over a period of twenty-one days. Mice that died within three days of challenge were excluded.

The results, of which some examples are shown in Table IV, indicated that the 30 strains tested were immunologically related.

TABLE IVA

Some Representative Results of Cross-Immunity Tests: Virulent Strains

Strain	*Proteus* OXK Agglutination Titre in Patient	Mortality in Mice Challenged with the Relevant Strain	
		Mice Convalescent from GAR	Mice Previously Uninoculated
POW	640	4/12	12/12
OBR	256	2/10	10/10
VAS	128	7/11	4/4
		7/12	3/3
CHO	20	4/12	11/11
STA	0	0/12	12/12

TABLE IVB

Some Representative Results of Cross-Immunity Tests: Mild and Intermediate Strains

Strain	*Proteus* OXK Agglutination Titre in Patient	Mortality in Mice Challenged with MIL	
		Mice Convalescent from the Relevant Strain	Mice Previously Uninoculated
UGA	640	4/11	5/6
WAR	320	0/11	5/6
GAR	160	2/13	13/13
HAM	0	0/12	12/12
FEL	0	9/12	6/6
		3/12	9/9
		3/12[1]	9/9[1]

[1] Challenged with VAS.

With about half of them complete protection was afforded under the conditions of the experiment, and none of the challenged mice

died. With the others protection was of high degree, although incomplete, except for the two strains FEL and VAS. With these the protection shown in the earlier tests was comparatively slight, and further investigation of their relationships is being made. (One strain, MAG, was lost before the immunity test was carried out. Infective mouse material had been stored for twelve days at about −15° C. and was then found inactive.)

Some evidence of the duration of immunity was obtained by the challenge of 69 mice that had been infected six to ten months previously. There were nine strains represented among the primary infections, and MIL was used for challenge, except for 11 mice challenged with MACK. Only three failed to survive, which indicated that the immunity in mice induced by an attack of scrub typhus persists for at least six months.

The specificity of the immunity was checked to the extent of challenging 12 mice convalescent from "Q" fever with MIL strain. All 12 died, which showed that primary infection with another species of rickettsia—*C. burneti*—had given no immunity to *R. tsutsugamushi*.

Scrub Typhus and Proteus OXK

The Weil-Felix test with *Proteus* OXK has played a valuable part in the routine investigation of North Queensland fever cases. We are greatly indebted to Dr. J. I. Tonge, Director of the Laboratory of Microbiology and Pathology, Brisbane, and his staff for carrying it out. Dr. Tonge (October 18, 1954) has provided this note on the technique:

Until the last ten months the organism used for the Weil-Felix test was a strain of *Proteus* OXK which was obtained from the Commonwealth Serum Laboratories, but at the present time we are using an organism "*Proteus mirabilis* II–OXK culture, No. 8309" obtained from the International Type Culture Collection at Colindale, England. When this latter strain was obtained from England a series of tests were carried out and it was found that there was no appreciable difference between it and the C.S.L. strain when used in the Weil-Felix test.

In carrying out the test serial dilutions of serum are made, starting at 1–8 (1–10 in earlier cases), and to each is added an equal volume of a bacterial emulsion in 0·2% formalin and 0·2% chloroform in 0·85% saline. The emulsion used has a density of approximately 2,000,000,000 organisms per mil. The test is carried out in agglutination tubes; incubation is overnight at 37° C. and the tests are read macroscopically the following morning.

In view of the fact that many sera showed no agglutination with this suspension, even though they came from proven cases of scrub typhus, it was decided to retest the sera with two other different suspensions. These were:

(*a*) A suspension prepared from *Proteus mirabilis* OXK as above from isolated colonies on phenol agar slopes. The suspension was alcoholized and of the same approximate density.

(*b*) An antigen prepared at the C.S.L. and supplied by Dr. J. L. O'Connor, batch No. 2194: an alcoholized suspension containing 0·02% formalin as a preservative prepared from *Proteus* XK "O". This suspension when received was concentrated but diluted to the same approximate density as the above two suspensions.

No significant difference was obtained in the results with these three different bacterial suspensions.

As regards the interpretation of agglutination with *Proteus* OXK, our experience inclines us to accept a titre of 1 : 80 as strongly suggestive of scrub typhus. However, this opinion is subject to certain qualifications. We have confirmed the observation of Lewthwaite and Savoor (1940) that the serum of occasional patients convalescent from leptospirosis may agglutinate *Proteus* OXK at this titre or higher.

Table V

Results of Weil-Felix Tests in 100 Cases each of Leptospirosis and "P.U.O."

Organism	Sera not Agglutinating at 1 : 20	Sera Agglutinating at Titres of		
		1 : 20	1 : 40	1 : 80
Proteus OXK:				
Leptospirosis	83	9	4	4
"P.U.O." ..	92	7	1	0
Proteus OX19:				
Leptospirosis	99	1	0	0
"P.U.O." ..	97	3	0	0

Table V shows the results of Weil-Felix tests in 100 cases of leptospirosis in which the diagnosis was established by culture; in four, the titre of *Proteus* OXK was 1 : 80. For comparison are shown the results in 100 cases of "P.U.O.", from which suspect cases of scrub typhus were excluded. A further reason for cautious interpretation is that titres up to 1 : 2560 for *Proteus* OXK have been found in persons in southern Queensland who have had no opportunity of acquiring scrub typhus (Tonge, 1953). In one of these the explanation was a urinary infection with *Proteus mirabilis*.

The results of the test in the 31 scrub typhus patients are included in Table I. In 16 cases titres of 1 : 80 or more were found. In seven further patients agglutinins were found in a titre (1 : 40 or less) which would not ordinarily be regarded as significant.

An important observation is that agglutinins for *Proteus* OXK were not found in the serum of eight patients. It should be noted that the exigencies of the fever investigations and the widely scattered location of the patients precluded examination of their sera at regular intervals, and it is possible therefore that a temporary rise in agglutinins may have occurred in some and been undetected. However, the sera of several of these patients, particularly HUG, FEL and HAM, were repeatedly examined (for the days, see Table I).

A number of previous observers have recorded that in some of their cases the result of the Weil-Felix test was negative. While in most of these the diagnosis of scrub typhus was clinical only, in those of Heaslip (1941) in North Queensland and of Smadel *et alii* (1950) in Malaya, the diagnosis had been established by mouse inoculation.

An analysis of our cases in which agglutinins for *Proteus* OXK were not found, in comparison with those in which they were present, showed no significant correlation with the locality where the patient was infected (Table III), with the patient's age or with the presence or absence of eschar (Table III).

With regard to the virulence for mice of the infecting strain (Table VI), it was noted that only one of eight strains isolated from " *Proteus*-negative " patients was virulent, whereas there were eight virulent strains among 16 isolated from patients with a titre of 1 : 80 or over.

It has been suggested that specific therapy may be an explanation of the failure to develop *Proteus* agglutinins. However, two patients in our series (CHO and MAL) who had insignificant titres or none at all, did not receive chloramphenicol, and the Weil-Felix titres of the patients of Smadel, Woodward *et alii* (1949) who were treated with chloramphenicol were quite comparable with those not so treated. Moreover, the existence of " *Proteus*-negative " patients was recognized in pre-antibiotic days.

Further observations by Smadel *et alii* (1952) provide the interesting suggestion that the phenomenon may be related to a previous attack of scrub typhus. Among their volunteers were five who had a second attack twelve to twenty-four months after the first. The reciprocal titres in convalescent sera after the first induced attack were 80, 640, 160, 40, 80, and after the second 20, 40, 80, 0, 0. Thus the second response was usually slight or absent and in every case less than the first. Although none of our " *Proteus*-negative " patients gave a history of a previous attack, its possibility cannot be excluded, for most of them had for years been exposed to the same environment.

An appreciation that an attack of scrub typhus may not be accompanied by the development of agglutinins for *Proteus* OXK clarifies the nature of a group of cases of " P.U.O." in North Queensland ; but it poses a further question—how may the diagnosis of these cases be verified in the laboratory? To the practitioner dealing with a clinically typical case this question may appear academic, but there are also mild and atypical cases, and apart from the desirability of scientific precision, there is the practical aspect of workers' compensation. In Queensland scrub typhus is compensatable when it has arisen in connexion with occupation, and the practice in such cases is to require laboratory confirmation of the diagnosis. The " *Proteus*-negative " patient is therefore in an anomalous position.

TABLE VI

Comparison of Weil-Felix Results in Man with Virulence for Mice[1]

Reciprocal Titre of *Proteus* OXK Agglutination	Virulence for Mice			Totals
	High	Intermediate	Mild	
80 or over ..	8	2	6	16
40 to 20	4	—	3	7
Less than 20 ..	1	2	5	8
Total strains	13	4	14	31

[1] The figures represent numbers of cases.

SUMMARY

Inoculation of mice with blood from 131 febrile patients in North Queensland resulted in the isolation of 31 strains of *R. tsutsugamushi* five of *C. burneti* and at least four of Leptospira.

The strains of *R. tsutsugamushi* varied considerably in their virulence for mice ; 13 were highly virulent, almost always killing the mice ; 14 were mild, rarely causing death ; four were intermediate in virulence.

Cross-immunity tests in mice showed that the strains of *R. tsutsugamushi* were immunologically related.

The failure to detect agglutinins for *Proteus* OXK in the serum of eight of 31 patients, and their insignificant titre in a further seven, draw attention to the need of a more sensitive laboratory test for scrub typhus.

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DIFFERENCES IN OPINIONS OF RADIOLOGICAL CHANGES IN PULMONARY TUBERCULOSIS[1]

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AMONG the most important indications of progress in pulmonary tuberculosis and of the effectiveness of treatment are the changes observed in serial radiographs of the chest. Interpretation of these changes, however, is a matter of personal appreciation, and sometimes different opinions will be given by different observers, particularly when the radiological changes are slight. This is of no serious consequence in clinical practice, so long as no major decisions affecting the welfare of patients are made on the basis of one observer's interpretation of films which may be interpreted differently by other observers. Nevertheless it is worth while recognizing the existence of observer-variation and eliminating it, or at least reducing it, whenever possible. It is particularly important to take it into account when the assessment of radiological changes is being used as one of the methods for measuring the efficacy of some form of treatment, as in controlled therapeutic trials. It was in this connexion that the present study was undertaken.

METHOD

Pairs of X-ray films (17 inches by 14 inches) were placed before each of six observers, who recorded simply whether there was radiological improvement, no change or deterioration. The observers were three radiologists and three physicians with extensive experience of pulmonary tuberculosis.

There were 98 films from 29 out-patients with chronic pulmonary tuberculosis. The films were arranged as 70 pairs to cover periods of two months (40 pairs of films) or four months (30 pairs), during which the patients were acting as controls or taking isoniazid in a controlled therapeutic trial (Calov *et alii*, 1954). The name of the patient, whether treated or control, and the interval between films were not disclosed to the observers. The pairs of films taken four months apart were shown to each observer a second time, at least a week later, mingled with other films. Thus the observers recorded their opinions in 100 viewings of 70 pairs of films which were presented to them in three weekly sessions.

Disagreements have been classified as major when completely opposite opinions were given—"improvement" as compared with "deterioration". All other disagreements have been classified as minor. In comparing the opinions given by two or more observers, four comparisons have been drawn from the films which were examined twice: the first report of one observer compared with the first report of the other, the first report of one with the second of the other, and so on. Wherever it was thought to be advisable the χ^2 test was applied and the 1% level of significance accepted.

TABLE I

The Consistency of Each Observer in Reporting Twice on the Films

Observer	Agreement (*per Centum*)	Disagreement (*per Centum*)	
		Major	Minor
A	70	4	26
B	50	20	30
C	53	7	40
Physicians' average	58	10	32
D	90	0	10
E	73	3	23
F	87	0	13
Radiologists' average	83	1	16
Average of all ..	71	5	24

RESULTS

Intra-Observer Variation

How consistent is an observer in the opinions he expresses? What are the chances that his opinion of the radiological changes shown in a pair of films will vary on different occasions?

[1] Received on October 7, 1954.

TABLE II

The Number of Times Any Observer Disagreed with Himself (Figures in Brackets) and with Each of the Other Observers[1]

Observer	Observer					
	A	B	C	D	E	F
A	[8 (1) 27]	70 (10) 153	72 (15) 153	53 (4) 153	56 (8) 153	55 (12) 153
B		[15 (6) 30]	76 (25) 160	81 (6) 160	77 (7) 160	78 (12) 160
C			[14 (2) 30]	79 (8) 160	73 (10) 160	74 (18) 160
D				[3 (0) 30]	46 (4) 160	66 (3) 160
E					[8 (1) 30]	58 (5) 160
F						[4 (0) 30]

[1] The figures show the total number of disagreements, then the number of major disagreements in parentheses, and the number of comparisons available for assessment in each instance. A, B and C are physicians and D, E and F, radiologists.

Our six observers were consistent in giving the same opinion twice in an average of 71% of the double viewings. In most instances in which an observer gave a different opinion when seeing films a second time, the variation was of a minor nature; that is, his interpretation varied between "improvement" or "deterioration" and "no change". In 5% of instances there was complete reversal of opinion. The measure of agreement and disagreement shown by each observer with himself is given in Table I. The actual numbers of times each observer disagreed with himself and with each of his colleagues are shown in Table II. If we examine only those comparisons in which a change in radiological appearances was recorded—that is, excluding those which were reported as showing no change at both viewings—then the same opinion was given twice by an observer in an average of 56% of the film-pairs. Once in every 12 times that he gave an opinion of radiological improvement or deterioration, he reversed his decision completely when reporting on the films a second time.

TABLE III

The Extent to which Each Observer Agreed or Disagreed with the Opinion Expressed by Any One of His Colleagues

Observer	Agreement (*per Centum*)	Disagreement (*per Centum*)	
		Major	Minor
A	60·0	6·4	33·6
B	51·8	7·6	40·6
C	52·8	9·6	37·6
D	59·0	3·2	37·8
E	60·9	4·3	34·8
F	58·2	6·3	35·4
Average ..	57·1	6·2	36·6

Inter-Observer Differences

If two or more observers are asked to give their opinions on radiological progress in a patient with chronic tuberculosis, what is the probability of their agreeing? Table II shows that no two observers agreed completely. A comparison of the opinions expressed by one observer with those of each of his colleagues in turn gives the results shown in Table III. In general two observers agreed in 57% of the 2365 comparisons of film-pairs and disagreed completely in 6%. If only those instances are taken in which one or other of a pair of observers reported some change, either improvement or deterioration, there was agreement between the two observers in 35% and complete disagreement in 8·5%.

There was unanimity of all six observers in 17% of comparisons (Table IV), of five or six observers in 41%, and of four or more in 77%.

TABLE IV

The Number of Times Agreement was Reached by Three or More Observers

Opinion	Number of Observers in Agreement					
	Six	Five or Six	Four or More	Three or More	Three Physicians	Three Radiologists
Improvement	9	18	26	32	17	13
No change	6	18	41	50	8	30
Deterioration	2	5	10	15	7	4
Total	17%	41%	77%	97%	32%	47%

Half or more of the observers were in agreement on almost every pair of films they judged.

Differences in Opinions of Physicians and Radiologists

The opinions given by physicians and radiologists differed significantly. Physicians disagreed with themselves (Table I) and among themselves (Table V) to a greater extent than

TABLE V

Differences in Opinions Among Pairs of Observers

Pairs of	Agreement	Disagreement	
		Major	Minor
Physicians ..	53	9	38
Radiologists ..	66	3	31

the radiologists. Similarly, there was unanimity among the physicians less frequently than among the radiologists (Table IV). These differences are associated with the fact that the

TABLE VI

The Radiologists said "No Change" More Often than the Physicians. These are Totals of Individual Opinions

Observers	Improvement	No Change	Deterioration
Physicians ..	123	105	68
Radiologists ..	98	171	31

physicians reported "no change" much less frequently than the radiologists (Table VI); the physicians' reports of change showed no bias towards optimism or pessimism. The

TABLE VII

The Relation Between the Majority Opinions of the Two Groups

Radiologists' Opinions	Physicians' Opinions			Total
	Improvement	No Change	Deterioration	
Improvement ..	36	5	0	41
No change ..	23	59	16	98
Deterioration ..	1	0	14	15
Total ..	60	64	30	154

opinions expressed by the majority of observers in the two groups show the same differences (Table VII). There was only one instance in which major disagreement occurred.

All the patients concerned in this study had had radiographs taken monthly, and these films had been reported on in the routine way. The impressions gained by an independent assessor of these routine reports are compared in Table VIII with the opinions given by the majority of the radiologists in the present study. There was agreement in 61% and major disagreement in 3%.

TABLE VIII

A Comparison of the Impression Given by Routine Reports from the X-ray Department During the Periods in Question and the Majority Opinion of the Three Radiologists Given in This Study

Majority Opinion of Radiologists	Interpretation of Routine X-Ray Reports		
	Improvement	No Change	Deterioration
Improvement ..	6	18	3
No change ..	7	52	5
Deterioration ..	0	6	3

DISCUSSION

The facts and figures which emerge from this study emphasize what we all recognize as existing, but rarely measure—that is, the variability attached to the subjective interpretation and measurement of clinical data. This, of course, is not unexpected, and is by no means confined to the assessment of radiographs. Discrepancies attributable to the observer have been demonstrated in many branches of medicine—for example, in taking histories of patients (Cochrane *et alii*, 1951), in eliciting physical signs in emphysema (Fletcher, 1952), in detecting cyanosis (Comroe and Botelho, 1947), in assessing the nutritional state of children (Jones, 1938), in the interpretation of bronchoscopic findings (Houghton and Joules, 1953), in the opinions given on microscopic sections (Cole, 1936), and even in the counting of red cells (Biggs and MacMillan, 1948). But the activity which has attracted most attention in this regard is the reading of chest radiographs.

The results of many tests with chest radiographs have shown that the likelihood of an observer changing his mind at a second reading of the films and the differences in opinions expressed by different observers are by no means inconsiderable (Birkelo *et alii*, 1947; Cochrane and Garland, 1952; Fletcher and Oldham, 1949; Garland, 1949; Groth-Petersen *et alii*, 1952; Miall *et alii*, 1953; Yerushalmy, 1947; Yerushalmy *et alii*, 1950). This is obviously important in everyday practice, and especially so in mass radiography surveys,

in which the smallness of the films is likely to provide an additional source of discrepancies (Shiels and Thomas, 1954). The efficiency with which a single observer selects films showing definite lesions from the films taken in a mass survey rarely exceeds 75%.

However, the present study is concerned rather with radiographic signs of progress of tuberculosis than with diagnosis, and is similar to the tests reported by Yerushalmy *et alii* (1951). These workers had three radiologists and three physicians give their opinions on the changes observed in 150 pairs of films. The observers were found to disagree with each other in almost one-third of the cases, and a single reader was likely to change his opinion at a second reading in one-fifth of the cases. When one observer reported improvement or deterioration, a second observer was likely to give the opposite opinion in 10% of cases, and then the first observer was found to reverse his first opinion in 7%. The radiologists frequently reported no change when the physicians reported improvement. These results are essentially similar to ours.

When the changes shown in serial radiographs clearly indicate resolution or extension of lesions, then an experienced observer will have no hesitation in giving his interpretation, his comments will be consistent however many times he is asked to report on the films, and we can expect that all other observers will agree with him. But when the changes are slight, as in many of our cases, or when extension of a lesion in one area is accompanied by resolution or collapse in another, then it is often difficult or even impossible to know, except perhaps in retrospect, whether the overall changes are for the better or for the worse. It becomes a matter of opinion, and differences of opinion can be expected. There is no method other than this subjective one for assessing the radiological change, so that the nearest we can get to the truth is to accept the consensus of opinion of a number of observers. To illustrate this from the present study, unanimity occurred among all six observers in less than one-fifth of the cases, but agreement was reached by three or more of the observers in almost every case. The value of consultation is obvious ; the more equivocal the changes, the greater the number of consultations required to interpret them. The importance to the patient and in the evaluation of therapy, as in clinical trials, needs no emphasis. If in our study the decision had been left to one observer, then in something less than one-fifth of the cases his opinion would have been confirmed by each of the other five observers. However, in almost one-third of the cases he would have given a different decision when consulted a second time, and his second opinion would have been just the opposite of the first for one out of every twelve pairs of films which he interpreted initially as showing improvement or deterioration.

Much the same degree of variation was found when films were read by two observers. Here there was disagreement between two observers in four cases out of every ten. When one observer reported a change in the radiological appearances, a second observer reported a change in the opposite direction in one case in every twelve. As might be expected of specialists operating in their own specialty, the radiologists were individually more consistent than the physicians and showed more agreement among themselves.

The magnitude of this variability in opinions is perhaps rather startling, but it reflects no discredit on the consultants taking part in this or other tests, nor on the art of interpreting chest radiographs in general. It just so happens that the reading of films is easily submitted to a test such as this. But there is no doubt that similar, and often greater, discrepancies exist in our interpretation of findings in other aspects of clinical medicine. Bedside discussions about cardiac murmurs are notoriously productive of differences in opinion. Fletcher found that eight experienced clinicians, Members or Fellows of the Royal College of Physicians, were in agreement scarcely more often than would be expected by chance on some of the simple signs they could elicit from an examination of chests. Observer-error is a natural concomitant of the subjective methods of assessment which form an important part of the clinician's art. As such, it is not a thing to be ashamed of or ignored. Rather should we encourage awareness of it, examine its magnitude and try to reduce it by improving our techniques. For example, Yerushalmy's results show that variation among observers is significantly less when the technical qualities of the films are uniform. Only by learning the magnitude of the variation attached to some of our methods shall we know how much reliance can be placed on the opinions given by ourselves and others. Consultation is most necessary on those questions which are likely to be vital to the welfare of the patient, and which are subject to a good deal of observer-variation. Furthermore, sympathetic consideration should be given to the opinion expressed by any student who is asked to use these methods in his examinations. As Fletcher (1954) puts it : " Until clinicians freely recognize

the bluntness of the instruments they use so assiduously, they will burden their students unnecessarily, deceive themselves, waste a lot of time and reach false conclusions from which their patients may suffer unnecessarily."

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SUMMARY

Three radiologists and three physicians gave their opinions of whether there was radiological improvement, deterioration or no change in 70 pairs of X-ray films of the chests of patients with chronic pulmonary tuberculosis taken two or four months apart. Thirty pairs of films were commented on a second time.

The extent to which each observer agreed or disagreed with his first opinion and with the opinions given by his colleagues is examined. The results are similar to those reported from other tests and emphasize the importance of observer-variation in the interpretation of radiographs and in other subjective methods of assessment.

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HÆMOCHROMATOSIS WITH HEART FAILURE COMPLICATING CONGENITAL NON-SPHEROCYTIC HÆMOLYTIC ANÆMIA[1]

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A COMPARATIVELY young woman was shown to have had a macrocytic non-spherocytic hæmolytic anæmia since birth; she ultimately developed hæmochromatosis with *diabetes mellitus*, and died from congestive heart failure with refractory œdema. In this communication observations on the interrelation of these three problems are recorded.

CASE REPORT

A housewife, aged thirty-four years, was admitted to hospital in September, 1953, with a short history of weakness, loss of weight, thirst and polyuria.

After her birth she was noted to be persistently jaundiced, and the liver was said to have been enlarged. There was no history of jaundice or anæmia in either of the parents, their relatives, or the two siblings. At the age of two years splenectomy was performed in view of splenic enlargement and jaundice. This did not appear to have any material effect on the hæmolysis, for as a child she tired easily and came to be regarded as delicate. When she was aged fifteen years she began to have attacks of biliary colic with exacerbation of jaundice, and a gall-bladder full of pigment stones was removed by Mr. James Ainslie.

She remained in tolerably good health, albeit pale and easily fatigued, until her first pregnancy at the age of twenty-five years. At the third month she was admitted to hospital with thrombophlebitis of a superficial vein of the right leg. She was found to be anæmic and was given blood transfusions (a total of four litres). A stillborn baby was born prematurely at the twenty-eighth week.

Two years later she was readmitted to hospital in the fourth month of her second pregnancy. Transient thrombophlebitis was again present. The hæmoglobin value was found to be 6·0 grammes *per centum*, and "macrocytic anæmia of pregnancy" was diagnosed. After failure to respond to treatment with liver and iron, further blood transfusions (four litres) were given. At the thirty-sixth week of pregnancy a live baby was delivered by Cæsarean section.

For the following six years she lived a moderately active life. Until her second pregnancy she had menstruated normally, but after that time menses ceased. In June, 1953, she began to feel unusually weak and tired, and suffered from thirst and polyuria. In the ensuing two months she lost 12 kilograms in weight. The day before her admission to hospital in September, she developed acute thrombophlebitis of the right saphenous vein.

The patient was a pale woman with greying hair. Slight scleral icterus was detectable. The face, arms and hands showed a slaty-brown pigmentation. The liver was enlarged six centimetres below the right costal margin. The heart was not enlarged, and no murmurs were present. The blood pressure was 150 millimetres of mercury, systolic, and 80 millimetres, diastolic. The urine contained both sugar and acetone, and a blood sugar concentration (fasting) estimated shortly after her admission to hospital was 300 milligrammes per 100 millilitres. Subsequent biochemical, histological and hæmatological investigations led to a diagnosis of hæmochromatosis and congenital macrocytic (non-spherocytic) hæmolytic anæmia.

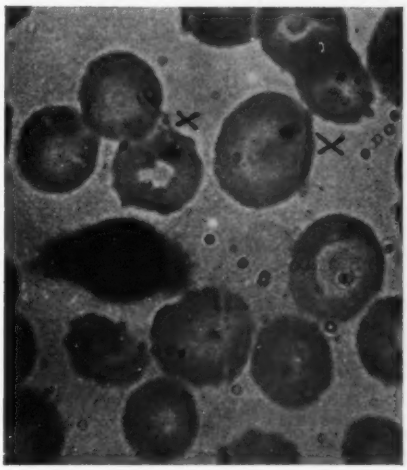

FIGURE I

Blood smear in case of non-spherocytic hæmolytic anæmia. The cells are macrocytic (mean corpuscular diameter 8·1 μ). Two red cells (X) contain basophilic Pappenheimer bodies (×1350)

With penicillin therapy the phlebitis subsided. The diabetes was controlled with 32 units of protamine zinc insulin and 20 units of soluble insulin in the morning and 24 units of soluble insulin in the evening. She was discharged from the hospital on November 6, 1953.

A month later, over the period of a week, she became extremely short of breath on exertion and developed considerable œdema of the ankles. She was readmitted to hospital on December 10 with severe congestive heart failure. Increased jugular venous pressure, ascites and œdema, triple rhythm, auricular fibrillation, low pulse pressure (blood pressure 110 millimetres of mercury, systolic, and 90 millimetres, diastolic) and

[1] Received on August 5, 1954.

signs of pulmonary congestion were present. A chest X-ray film indicated considerable cardiac enlargement, pulmonary congestion and effusion of fluid into the right pleural cavity.

She was given " Digoxin " and injections of mersalyl twice a week. The daily salt intake was restricted to between 250 and 500 milligrammes. There was no reduction in the signs of cardiac failure. A week after

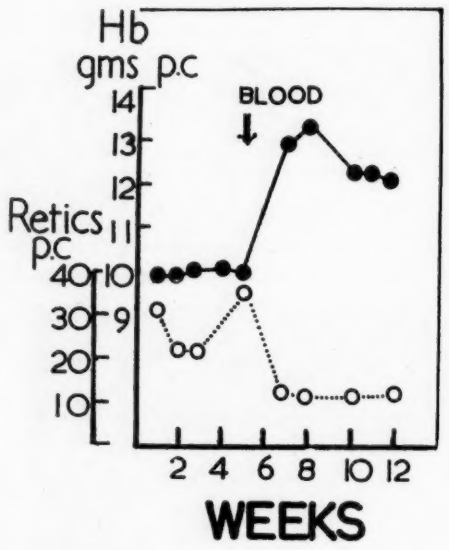

FIGURE II

Levels of hæmoglobin and reticulocytes following the transfusion of 1500 millilitres of blood to patient with non-spherocytic hæmolytic anæmia

her admission to hospital she began to vomit and had diarrhœa. She felt extremely languid and strongly disinclined to eat. Her urinary output diminished, and her œdema and weight increased. Feeding became a difficult problem, for she tolerated intragastric intubation very poorly. Periodic checks on her blood sugar content and urine indicated no worsening of her diabetic status; she remained well controlled on a total of 74 units of insulin daily. In a waterlogged orthopnœic state she died on January 11, 1954.

Hæmatological Investigations

On her admission to hospital in September, 1953, the red blood cell count was 2,300,000 cells per cubic millimetre, 28% being reticulocytes. The hæmoglobin value was 8·8 grammes *per centum*. The serum

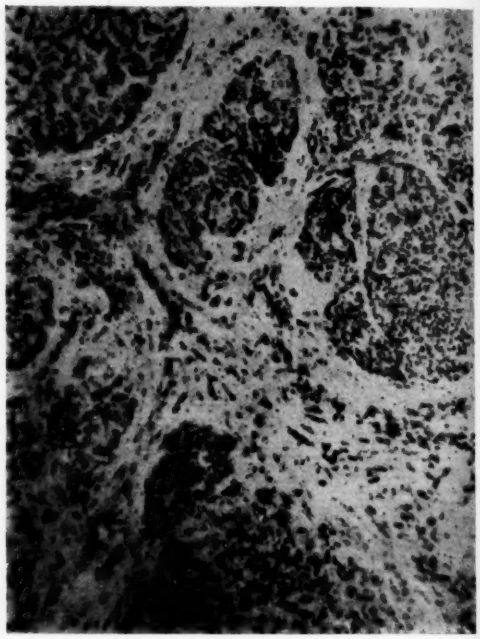

FIGURE III

Liver biopsy showing iron pigment deposited in fibrous tissue and the parenchymal cells of the pseudolobules. (Prussian blue reagent uncounterstained. ×39)

bilirubin level was 1·8 milligrammes per 100 millilitres. The following absolute values were obtained: hæmatocrit, 28%; mean corpuscular volume, 121 cubic μ; mean corpuscular hæmoglobin, 38 micromicrogrammes; mean corpuscular hæmoglobin concentration, 31%; mean corpuscular diameter, 8·1 μ.

Examination of blood films showed that the red cells were of uniformly macrocytic appearance. About

TABLE I

Results of Serial Tests of Liver Function

Date	Serum Bilirubin. (Milligrammes per 100 Millilitres)	Serum Alkaline Phosphatase. (King-Armstrong Units)	Thymol Turbidity.[1]	Thymol Flocculation.[2]	Serum Albumin Content. (Grammes *per Centum*)	Serum Globulin Content. (Grammes *per Centum*)
5.10.53	0·6	11·9	2	0	—	—
29.10.53	1·8	11·2	3	+++	3·55	3·95[3]
17.12.53	2·8	9·5	1	0	3·5	3·5
31.12.53	3·2	19·0	2	0	3·1	4·2

[1] Normal, 0 to 3 units.
[2] Normal, 0.
[3] Fractionated serum globulin (grammes *per centum*): α, 1·15 grammes; β, 0·56 gramme; γ, 2·24 grammes.

10% of red cells contained basophile-staining Pappenheimer bodies (Figure I) (Pappenheimer *et alii*, 1945). The bone marrow was hyperplastic and erythroid cells predominated: erythropoiesis was of normoblastic type.

The Coombs test (both direct and indirect) produced a negative result. The response to the Wassermann test was negative. Cold agglutinins were not detected in the serum.

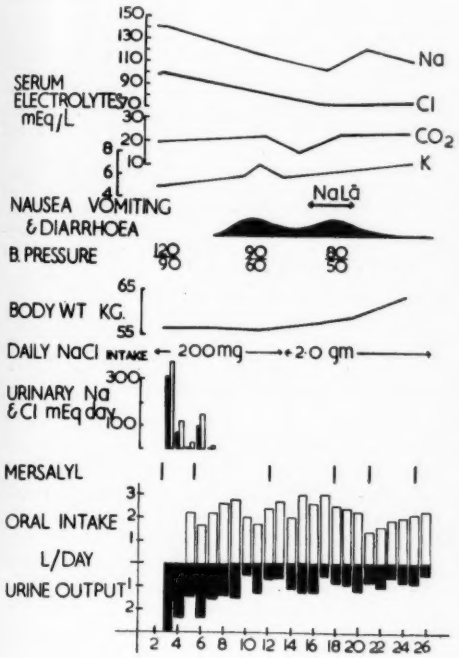

FIGURE IV

Data on fluid balance, serum electrolytes, and body weight during patient's final hospital admission

The osmotic fragility of freshly drawn blood and of defibrinated blood incubated at 37 °C. for twenty-four hours was studied by the method described by Dacie and his colleagues (1953). The osmotic fragility of the patient's fresh cells was slightly diminished in comparison with controls, hæmolysis commencing in 0·4% saline and being complete in 0·2% saline (complete in 0·3% saline in the control). On the other hand, osmotic fragility of test cells was slightly increased in comparison with control cells after overnight incubation, hæmolysis commencing in 0·6% saline (control 0·5%).

The rate of spontaneous hæmolysis of the patient's red cells was studied in two-millilitre samples of defibrinated blood. After incubation for twenty-four hours at 37° C., the amount of liberated hæmoglobin in supernatant serum after centrifugation was compared with that obtained from normal blood similarly treated. The amount of autohæmolysis of the patient's cells was in excess of that of controls (seven " units ", in comparison with three and four arbitrary units in controls).

The qualitative test for urinary porphobilinogen produced a negative result, and there was no excess of uroporphyrin in the urine.

Abnormal hæmoglobin was not present in the red cells of the patient. The resistance of hæmoglobin to alkaline denaturation (method of Singer *et alii*, 1951) was investigated by Dr. Carl de Gruchy, of Melbourne. A normal alkaline denaturation value of 7·2% was obtained. Paper electrophoresis of hæmoglobin gave a normal pattern.

FIGURE V

Section of adrenal cortex showing atrophic changes and deposition of iron pigment in *zona glomerulosa*. (Hæmatoxylin and eosin stain, ×232)

Quantitative studies of the survival of transfused normal cells were not undertaken. Dacie and his colleagues (1953) have adduced evidence that in a case of hæmolytic anæmia similar to our own transfused cells survived longer than in normal recipients. The curve of hæmoglobin and reticulocyte levels in this patient following the transfusion of a litre and a half of blood would appear to indicate that survival of transfused cells was not diminished and that a temporary diminution in output of abnormal macrocytes was induced (Figure II).

Liver Function

Minor abnormalities were noted in serial biochemical tests of liver function (Table I). Liver biopsy showed gross fibrosis. Massive deposits of Prussian blue staining material were present in both fibrous tissue and the parenchymal cells of the pseudolobules (Figure IV).

The Œdema

Fluid balance, weight and serum electrolyte values during the last admission of the patient to hospital are shown in Figure IV. During the previous two months she had been eating an ordinary diet with only moderate restriction of carbohydrate. With the onset of congestive heart failure the daily intake of salt was reduced to 300 milligrammes. At first mersalyl provoked a satisfactory diuresis, but later was wholly ineffective. Vomiting and diarrhœa were accompanied by signs of peripheral circulatory failure and severe hyponatræmia and hypochloræmia was found to be present (serum sodium content, 106 milliequivalents per litre; serum chloride content, 78 milliequivalents per litre). At the same time the patient was acidotic (carbon dioxide content, 16 milliequivalents per litre), and the level of serum potassium was high (rising to 7·8 milliequivalents per litre). Elevation of daily salt intake and the administration of sodium lactate caused some improvement in the serum electrolyte picture, but she remained refractory to mercurial diuretics, and her weight continued to increase prior to death.

FIGURE VI

Section of myocardium showing deposition of iron pigment in cardiac muscle with associated vacuolization and loss of normal striation, interstitial fibrosis, and nuclear abnormalities—giant enlargement and hyperchromatism. (Hæmatoxylin and eosin stain, ×378)

Autopsy Findings

At autopsy the body was grossly œdematous. Free fluid was present in the abdomen and in both pleural cavities. All chambers of the heart were greatly dilated, but the heart valves and coronary arteries were normal in appearance. The myocardium showed brown pigmentation. The lungs were œdematous. The liver was grossly enlarged, showed bronze pigmentation, and was finely cirrhotic. The pancreas also was cirrhotic and pigmented. Enlarged pigmented lymph nodes were present in the *porta hepatis* and along the course of the abdominal aorta. The kidneys showed congestive changes only.

Microscopically heavy deposits of hæmosiderin were present in the characteristic sites—skin, liver and pancreas. Very faint deposits were discernible in the distal collecting tubules of the kidney. The α cells of the anterior lobe of the pituitary and the cuboidal cells lining the follicles of the thyroid gland contained cytoplasmic deposits of hæmosiderin. In the adrenal glands deposits of iron were localized in the *zona glomerulosa* (Figure V).

Changes in the myocardium were striking. There was diffuse deposition of pigment in muscle fibres (Figure VI) with associated degenerative changes—loss of striation, hyaline change and bizarre appearances of the nuclei. The amount of interstitial connective tissue was considerably increased.

DISCUSSION

It is reasonable to relate the three major clinical manifestations — hæmolysis, hæmochromatosis and heart failure—in this case.

The Nature of the Anæmia

Thompson, in 1939, referred obliquely to three families with non-spherocytic hæmolytic anæmia, and within recent years more refined diagnostic techniques have brought to light several further examples of atypical congenital hæmolytic anæmia. In the three families described by Haden (1947) the red cells were macrocytic. In families described by Kaplan and Zuelzer (1950) and by Crosby (1950), red cell abnormality was linked with anomalies of bone development and porphyria. Dacie *et alii* (1953) have gathered together a series of cases of atypical hæmolytic anæmia, and have been able to separate a group of cases which had the following characteristics: (*a*) the hæmolysis had been occurring since the patient's birth; (*b*) the red cells were macrocytic; (*c*) the red cells displayed slightly diminished osmotic fragility in the freshly drawn state, but increased fragility when incubated at 37° C. for twenty-four hours; (*d*) they contained so-called Pappenheimer bodies—small basophilic granules 1 to 2 μ in diameter; (*e*) unlike cases of acholuric jaundice, splenectomy did not relieve the anæmia.

It is considered that the present case—in respect of which there seems to be no alternative but to use the morphologically descriptive term of " congenital non-spherocytic macrocytic hæmolytic anæmia "—fulfils the criteria of Dacie and his colleagues.

The Development of Hæmochromatosis

It is usual to differentiate between endogenous hæmochromatosis, an inherited anomaly of iron metabolism (Sheldon, 1935), and exogenous hæmochromatosis complicating the administration of multiple transfusions given for refractory anæmia (Kark, 1937; Schwarz and Blumenthal, 1948; Wyatt *et alii*, 1950; Aufderheide *et alii*, 1953). Several factors considered together—notably the comparative youth of the patient, the sex, and the absence of family history—exclude the likelihood of a diagnosis of endogenous hæmochromatosis. The massive siderosis was evidently related to chronic hæmolysis, and it is of interest that there have been several recent reports of hæmochromatosis complicating other chronic hæmolytic states—for example, sickle cell anæmia (Frumin and Mills, 1953) and Cooley's anæmia (Howell and Wyatt, 1953; Currin, 1954; Ellis *et alii*, 1954). Until recently it has been tacitly assumed that the iron deposited in excess in the tissues in subjects of aplastic anæmia receiving multiple transfusions was derived from the iron in the transfused blood. However, Dubach *et alii* (1948) and Muirhead and his colleagues (1949) have demonstrated that intestinal iron absorption is increased in patients with aplastic anæmia, hæmolytic anæmia and pernicious anæmia; and Stewart *et alii* (1953) have made similar observations in dogs rendered anæmic with phenylhydrazine over prolonged periods. In our patient the amount of iron present in the tissues was greatly in excess of the amount of iron present (approximately six grammes) in the blood transfusions (approximately 11 litres) received during her lifetime; alimentary absorption of iron considerably in excess of physiological requirements must therefore have occurred over a long period. The fact that she had not menstruated for several years may have facilitated the development of siderosis in latter years. The case thus exemplifies the concept that chronic anæmia in some manner modifies the "mucosal block" against the intestinal absorption of iron. The medicinal use of iron in chronic hæmolysis is therefore contraindicated, since it may hasten the development of hæmochromatosis (Clough, 1952; Wallerstein and Robbins, 1953).

The sites of deposition of hæmosiderin in this case did not differ from those observed in classical endogenous hæmochromatosis (Althausen *et alii*, 1951). The heavy deposition of hæmosiderin in the anterior lobe of the pituitary, the thyroid and the adrenal cortex inevitably raises the question of whether the deposition of iron pigment in cytoplasm interferes with the elaboration of hormones by the specific cells of endocrine glands. The hypogonadism, impotence and diminished urinary excretion of 17-ketosteroids may be taken as evidence of hypopituitarism, and some authors, particularly on the continent (de Véricourt, 1936; Nussbaumer *et alii*, 1952), have maintained that melanotic pigmentation, hypotension and asthenia are manifestations of adrenal cortical insufficiency. In the present case, the high level of serum potassium occurring in conjunction with hyponatræmia and hypochloræmia led to consideration of the possibility that adrenal insufficiency played a role in the causation of the distorted serum electrolyte picture. This hypothesis appeared to be confirmed by the finding of massive pigmentation and what were interpreted as atrophic changes in the *zona glomerulosa*. Were it proven that mineralocorticoids are elaborated only in this zone, then this view might be acceptable; but in rats Chester Jones and Wright (1954) have recently shown that physiological adrenocortical secretions are probably produced in the *zona fasciculata* rather than the outer zone.

Heart Failure

In the absence of all other provocative causes (rheumatic heart disease, coronary heart disease, severe anæmia), congestive heart failure was attributable to myocardial insufficiency due to extensive siderosis; there was histological evidence that stainable iron had caused focal muscle degeneration and interstitial fibrosis. There is an extensive literature on cardiac involvement in hæmochromatosis (Blumer and Nesbit, 1938; Petit, 1945; Tucker *et alii*, 1948) which has been reviewed by Swan and Dewar (1952). Arrythmias and conduction defects are common electrocardiographic findings. This case indicates a characteristic feature of pigment myocarditis, that once congestive failure supervenes patients are unlikely to survive long.

The cause of the extreme hyponatræmia (the "low sodium syndrome") in this patient invited speculation. Dilution of extracellular sodium in both congestive heart failure and liver cirrhosis has been postulated as being due to excessive water retention caused by increased amounts of antidiuretic substances detectable in urine (Bercu *et alii*, 1950; Ralli *et alii*, 1945). Antidiuretic hormone excess in cirrhosis and heart failure has been denied, however, by Stein *et alii* (1954). Whatever factors are involved in the causation of hepatic and cardiac œdema—impaired renal function, disordered

corticosteroid metabolism, increased antidiuretic hormone concentration, ferritin activity—it is reasonable to suppose that they are capable of summation, as in this patient in whom both myocardial insufficiency and advanced cirrhosis were present. The occurrence of severe metabolic acidosis was attributed to the combined effect of diabetes and protein catabolism, and the severe impairment of renal function known to be present in the low sodium syndrome (see Leiter *et alii*, 1953). The hyperkalæmia was less easily explained. At least four mechanisms could be postulated: adrenal cortical insufficiency, intracellular potassium depletion resulting in a shift of potassium into the extracellular compartment, renal insufficiency, and the blockage of tubular excretion of potassium by mercurial diuretics (Berliner *et alii*, 1951).

SUMMARY

A description is given of clinical, laboratory and autopsy findings in a woman, aged thirty-five years, with non-spherocytic congenital hæmolytic anæmia, who developed hæmochromatosis with *diabetes mellitus* and died of heart failure.

The organs contained massive deposits of hæmosiderin in the sites usual in hæmochromatosis. Particularly noteworthy was the presence of pigment in the *zona glomerulosa* of the adrenal cortex and in the myocardium, which showed in addition degenerative changes and interstitial fibrosis.

The amount of iron in the tissues was considerably in excess of that given by blood transfusion, which implies that excessive intestinal absorption had been taking place.

ACKNOWLEDGEMENTS

We are grateful to Dr. N. Kovacs for helping with the hæmatological investigations, to Dr. T. Lubbe who performed the autopsy examination, and to Dr. D. H. Curnow and his associates for performing the biochemical investigations in this case. Mr. R. Van Raalte prepared the photomicrographs.

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PULMONARY FUNCTION IN NORMAL SUBJECTS[1]

I. VENTILATORY ASPECTS AND DISTRIBUTION OF GAS IN THE LUNGS OF NORMAL SUBJECTS

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THIS investigation deals with a series of selected tests of pulmonary function performed on a group of healthy young adults, and is intended as a control for later studies on patients with mitral stenosis. The data so obtained have been compared with those of Hurtado and Boller (1933), of Hurtado *et alii* (1934), of Robinson (1938) and of Richards (1948), also derived from normal subjects of similar age.

By the use of the methods described by Baldwin *et alii* (1948) with certain modifications, the following assessments of pulmonary ventilation and gas distribution were made: vital capacity and its subdivisions, functional residual capacity and its derivatives, maximum breathing capacity and an index of intrapulmonary mixing. The group investigated consisted of ten subjects of each sex, members of the staff of the Hallstrom Institute of Cardiology and medical students—all aged between twenty and thirty-five years. A full discussion of the classification of pulmonary insufficiency and the application of these tests of pulmonary function has been given by Baldwin *et alii* (1948).

DEFINITIONS

For subdivisions of lung volume the definitions of Pappenheimer (1950) have been followed, while for resting total pulmonary and alveolar ventilations those of Comroe (1951) have been used. Residual capacity has been estimated as the difference between the functional residual capacity and the reserve air.

Maximum breathing capacity (Hermannsen, 1933) is the maximum volume of air that can be moved in and out of the chest per minute by voluntary effort. It is usually measured over a period of fifteen seconds and is expressed in litres per minute.

Index of intrapulmonary mixing (Cournand *et alii*, 1941) is the percentage of nitrogen in the end-expiratory alveolar gas after pure oxygen has been breathed for seven minutes under basal conditions.

METHODS

The procedures which were used to make the present assessments are as follows:

Vital Capacity and its Subdivisions.

The measurements of vital capacity, reserve air and complemental air were made on the subject immediately after the functional residual capacity determinations. Thus the metabolic state was basal and the posture standardized (supine, head and shoulders raised to a height of about two pillows, on a plane inclined about 25° from the horizontal portion of the bed).

The apparatus consisted of a nine-litre spirometer[1] with the absorbent cannister and flutter valve removed, and an electrically driven kymograph. Connexions were made with rubber hose of an internal diameter of one inch. A rubber mouthpiece and sponge rubber nose-clamp were used.

The subject was connected to the spirometer which had been three-quarters filled with room air, several quiet respirations were recorded, and spirographic tracings were obtained for the estimation of reserve air and vital capacity. This was repeated once, then a similar tracing was made for complemental air and vital capacity. The instrument was flushed out with air between determinations. The vital capacity was taken as the greatest of the three estimates and the reserve air as the mean of the two estimates.

[1] Work done under a grant-in-aid to the Hallstrom Institute of Cardiology from the Life Insurance Medical Research Fund of Australia and New Zealand.

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[1] Instruments supplied by Warren E. Collins Inc., Boston, Mass., and by Palmer, Ltd., London, were employed.

Maximum Breathing Capacity.

Immediately after each of two determinations of vital capacity the subject was required to breathe as quickly and deeply as possible for a period of fifteen seconds. It was found that emphasis on the rate of breathing alone, recommended by Cournand *et alii* (1939), did not always produce the highest estimate. An experienced observer, watching the spirogram, could give suitable instructions to the subject to alter the rate and depth of breathing and thus increase the rate of ventilation. The higher of the two ventilation figures obtained over periods of fifteen seconds from an analysis of the spirogram, expressed in litres (at body temperature and ambient barometric pressure and saturated with water vapour) per minute, was recorded as the maximum breathing capacity.

Details of procedure for the determination of the vital capacity and its subdivisions and the maximum breathing capacity are described by Baldwin *et alii* (1948).

Functional Residual Capacity and Index of Intrapulmonary Mixing.

The open circuit method of Darling *et alii* (1940) was employed for the estimation of the functional residual capacity and the index of intrapulmonary mixing. The technique has been described in detail by Baldwin *et alii* (1948). The principle of the method is as follows: Oxygen is breathed by the subject for a period of seven minutes, commencing at the end of a normal expiration. The expired gas is collected in a gasometer, and the volume of nitrogen which has been removed from the lungs is estimated. When due allowance is made for nitrogen (i) which is still present in the lungs at the end of the determination, (ii) which has diffused from the blood into the lungs during the procedure and (iii) which has entered the system from the oxygen cylinder, the functional residual capacity may readily be calculated.

It is necessary to obtain a sample of gas from the gasometer, and an alveolar sample (collected by the Haldane technique), at the end of the seven-minute period. The latter is analysed for nitrogen and carbon dioxide contents, and the former in duplicate for nitrogen content, by means of a Haldane type gas analyser. The index of mixing is equal to the percentage of nitrogen in the alveolar sample, corrected for nitrogen present in the cylinder oxygen (this varied in concentration from zero to 1·04%).

An investigation into the reproducibility of the method led to various modifications of apparatus and procedure, and will be described in a later paper of this series. A discussion of errors of duplicates for gas analyses and for estimates of functional residual capacity and index of intrapulmonary mixing will be included here.

An approximate estimate of resting total pulmonary ventilation has been made from the spirogram obtained from each subject during the first stage of the determination.

CALCULATION

The actual equation for the calculation of the functional residual capacity follows from the principle described already, but incorporates additional corrections. Thus:

> N_2 expired into the gasometer during the determination $= N_2$ originally in the lungs $+ N_2$ added from the O_2 cylinder $+ N_2$ which has diffused from the blood into alveolar gas during the seven minutes.

Consequently the functional residual capacity is equal to:

$$\left(\frac{\text{volume of } N_2 \text{ washed into the gasometer from the lungs}}{\text{change in } N_2 \text{ concentration in alveolar gas}}\right)$$

Corrections have been made as follows: (i) to express volumes at body temperature and ambient barometric pressure and saturated with water vapour, (ii) for the dead space of the apparatus (30 millilitres), (iii) for any displacement from the mean end-expiratory position for quiet breathing at the moment the subject commences to breathe oxygen.

Cournand *et alii* (1941) demonstrated that in practice the initial percentage of nitrogen in alveolar air is equal to 81%±1%, and the figure 81 is therefore employed in these calculations.

MEASUREMENTS AND DISCUSSION

General

All gas volumes are expressed in litres at body temperature, at ambient barometric pressure and saturated with water vapour. Estimates have not been omitted merely because they appear to differ excessively from mean values.

The results of the ventilatory tests are classified in Table I (for males and females), and are compared with data from normal

TABLE I

Lung Volume and Ventilation Data from Groups of Normal Male and Female Subjects within the Age Group Eighteen to Thirty-Five Years (in the Supine Posture)

Observation	Males				Females		
	Present Series	Hurtado and Boller[1]	Richards	Robinson	Present Series	Hurtado *et Alii*[1]	Richards
Age (Years):							
Mean	23·9	22·9	25·5	24·0	24·5	23·1	25·1
Standard deviation	4·6	3·3	6·0	—	4·4	3·4	6·2
Range	20–34	18–30	16–34	20–29	20–35	18–34	15–34
Height (Centimetres):							
Mean	175·0	176·2	173·8	180	163·5	163·4	161·8
Standard deviation	5·7	5·1	8·6	—	5·0	4·2	6·2
Range	168–183	158–187	150–182	170–188	157–175	152–178	154–172
Weight (Kilograms):							
Mean	71·5	72·5	66·0	72·9	55·4	57·2	59·2
Standard deviation	12·5	11·2	8·3	—	4·0	9·4	11·1
Range	59·0–98·2	52·8–104·0	52·5–86·0	63·4–84·4	48·6–59·9	42–83·2	44·0–84·0
Surface Area (Square Metres):							
Mean	1·84	1·88	1·77	1·91	1·59	1·60	1·58
Standard deviation	0·15	0·13	0·14	—	0·07	0·14	0·14
Range	1·66–2·14	1·52–2·19	1·55–2·07	1·74–2·10	1·47–1·71	1·36–1·89	1·39–1·94
Residual Capacity (Litres):							
Mean	1·17	1·19	—	1·66	0·86	1·10	—
Standard deviation	0·29	0·35	—	—	0·22	0·30	—
Range	0·62–1·45	0·56–1·98	—	0·84–2·94	0·47–1·10	0·53–2·26	—
Reserve Air (Litres):							
Mean	1·07	0·98	0·88*	1·39	0·75	0·73	0·64
Standard deviation	0·17	0·26	0·20*	—	0·25	0·19	0·20
Range	0·76–1·27	0·26–1·58	0·52–1·46*	0·95–1·83	0·44–1·12	0·28–1·42	0·18–1·05
Functional Residual Capacity (Litres):							
Mean	2·24	2·18	—	3·05	1·60	1·82	—
Standard deviation	0·39	0·50	—	—	0·41	0·39	—
Range	1·73–2·69	0·96–3·09	—	1·91–4·45	0·91–2·12	1·15–3·10	—
Complemental Air (Litres):							
Mean	3·73	3·79	—	—	2·85	2·42	—
Standard deviation	0·67	0·52	—	—	0·22	0·36	—
Range	2·73–4·63	2·41–4·93	—	—	2·63–3·19	1·70–3·32	—
Vital Capacity (Litres):							
Mean	4·91	4·78	4·01*	5·25	3·64	3·14	3·06†
Standard deviation	0·70	0·59	0·62*	—	0·53	0·41	0·55†
Range	3·52–5·60	3·40–5·85	2·79–4·95*	4·20–6·03	2·85–4·25	2·28–3·95	2·31–4·15†
Vital Capacity as Percentage of Predicted Value:							
Mean	112	108[2]	93*[2]	117[2]	115	99[2]	98†[2]
Standard deviation	14	—	—	—	14	—	—
Range	84–133	—	—	—	98–136	—	—
Total Capacity (Litres):							
Mean	6·07	5·97	—	6·81	4·50	4·24	—
Standard deviation	0·88	0·81	—	—	0·65	0·57	—
Range	4·40–6·98	4·25–7·68	—	5·04–8·37	3·61–5·28	3·20–6·18	—
Reserve Air as Percentage of Vital Capacity:							
Mean	22·7	20·6	20·6*	26[2]	20·1	22·9	20·4
Standard deviation	3·9	5·4	—	—	4·7	4·6	—
Range	14·4–27·8	5·9–36·9	—	—	14·0–28·7	7·8–35·9	—
Residual Capacity as Percentage of Total Capacity:							
Mean	19·1	19·8	—	23·7	18·9	25·9	—
Standard deviation	3·6	4·4	—	—	3·9	5·0	—
Range	10·5–24·3	10·3–29·7	—	17–35	13·0–25·0	14·1–36·6	—

The number of subjects in each group is as follows: present series, 10 males, 10 females; Hurtado and Boller, 50 males; Hurtado *et alii*, 50 females; Richards, 18 males, 17 females; Robinson, 11 males.

When a particular observation has not been made on a whole group, the number of subjects studied is indicated in the table thus: *=17 subjects; †=16 subjects; ‡=15 subjects.

[1] The figures for residual capacity and estimates derived from them incorporate corrections to the original figures of Hurtado and Boller (1933) and of Hurtado *et alii* (1934), made by Kaltreider *et alii* (1938) to allow for diffusion of nitrogen from the blood into the lungs.

[2] Calculated as the ratio of corresponding mean values.

[3] Calculated from the mean measured value and from mean figures for physical characteristics. Analysis, by the use of estimated coefficients of variation of the two components of each ratio (2) and (3) and a very rough estimate of the coefficient of correlation between them, shows that the calculated ratio is a close approximation to the true value on the original data, with one exception—the maximum breathing capacity expressed as a percentage of the predicted value. It is a particularly close approximation for the resting ventilation per unit body surface area.

[4] Determinations made in the standing posture, stated by Baldwin *et alii* (1948) to give 3% to 5% higher figures than when supine.

TABLE I (*continued*)

Lung Volume and Ventilation Data from Groups of Normal Male and Female Subjects within the Age Group Eighteen to Thirty-Five Years (in the Supine Posture) (continued)

Observation	Males				Females		
	Present Series	Hurtado and Boller[1]	Richards	Robinson	Present Series	Hurtado *et Alii*[1]	Richards
Functional Residual Capacity as Percentage of Total Capacity (Litres):							
Mean	36·9	36·2	—	45[2]	35·0	43·0	—
Standard deviation	4·3	5·4	—	—	5·2	5·6	—
Range	29·2–45·1	19·0–46·9	—	—	25·2–42·0	27·5–52·3	—
Maximum Breathing Capacity (Litres per Minute):							
Mean	135	—	126*[4]	—	100	—	93·7‡[4]
Standard deviation	35	—	29*	—	18	—	12·6‡
Range	72–189	—	82–169*	—	60–119	—	64–118‡
Maximum Breathing Capacity as Percentage of Predicted Value:							
Mean	105	—	97*[3]	—	107	—	100‡[3]
Standard deviation	19	—	—	—	16	—	—
Range	75–134	—	—	—	71–128	—	—
Resting Respiratory Rate per Minute:							
Mean	13	—	—	—	13	15	—
Standard deviation	3	—	—	—	3	2	—
Range	9–16	—	—	—	8–18	—	—
Resting Tidal Volume (Litres):							
Mean	0·50	—	—	—	0·44	0·48	—
Standard deviation	0·10	—	—	—	0·09	0·14	—
Range	0·36–0·65	—	—	—	0·34–0·57	0·30–0·98	—
Resting Ventilation (Litres per Minute):							
Mean	6·4	—	—	—	5·4	6·9	—
Standard deviation	0·7	—	—	—	0·5	1·5	—
Range	5·6–7·4	—	—	—	4·4–6·5	—	—
Resting Ventilation per Unit Body Surface Area (Litres per Minute per Square Metre):							
Mean	3·5	—	3·6*	—	3·4	4·3[3]	3·2
Standard deviation	0·5	—	0·3*	—	0·3	—	0·4
Range	2·7–4·1	—	3·1–4·5*	—	2·8–3·8	—	2·6–4·3

The number of subjects in each group is as follows: present series, 10 males, 10 females; Hurtado and Boller, 50 males; Hurtado *et alii*, 50 females; Richards, 18 males, 17 females; Robinson, 11 males.

When a particular observation has not been made on a whole group, the number of subjects studied is indicated in the table thus: * = 17 subjects; † = 16 subjects; ‡ = 15 subjects.

[1] The figures for residual capacity and estimates derived from them incorporate corrections to the original figures of Hurtado and Boller (1933) and of Hurtado *et alii* (1934), made by Kaltreider *et alii* (1938) to allow for diffusion of nitrogen from the blood into the lungs.

[2] Calculated as the ratio of corresponding mean values.

[3] Calculated from the mean measured value and from mean figures for physical characteristics. Analysis, by the use of estimated coefficients of variation of the two components of each ratio (2) and (3) and a very rough estimate of the coefficient of correlation between them, shows that the calculated ratio is a close approximation to the true value on the original data, with one exception—the maximum breathing capacity expressed as a percentage of the predicted value. It is a particularly close approximation for the resting ventilation per unit body surface area.

[4] Determinations made in the standing posture, stated by Baldwin *et alii* (1948) to give 3% to 5% higher figures than when supine.

subjects of similar age, varying from eighteen to thirty-five years, reported by Hurtado and Boller (1933), by Hurtado *et alii* (1934), by Richards (1948) and by Robinson (1938).

Physical Characteristics

In the present series, a fairly wide range of physical characteristics is represented except for the weights and body surface areas of the female subjects. The mean values and the dispersions, other than the two just mentioned, of the ages and physical characteristics for each sex correspond well with those found by Hurtado and Boller, by Hurtado *et alii*, and by Richards.

Robinson's group show higher mean values for weight, body surface area, and in particular height, than any other in Table I. The differences in height were sufficient to warrant statistical analysis. An estimate of the standard deviation of Robinson's figures was made from their range (Dixon and Massey, 1951) and the efficiency of this estimate (83%) was taken into account. The analysis showed no significant differences among the heights of the first three groups, but there was a significant difference between the first three groups, considered as a whole, and Robinson's group ($P<0{\cdot}02$). It is therefore doubtful that the latter should be used for purposes of comparison in relation

to the population from which the first three samples were drawn, unless corrections for height can be made.

Ventilatory Data

For the most part there is good agreement between the figures presented and those of Hurtado and Boller, of Hurtado *et alii*, and of Richards. However, Robinson's mean values are mostly considerably higher, and it follows from the previous discussion that only one of his figures can be compared with those of the other investigators—namely, the mean value of the vital capacity expressed as a percentage of its predicted value, which is calculated from height (in this case it is an approximation only).

TABLE II

Prediction Formulæ Used (Baldwin et alii, 1948)[1]

Quantity Estimated	Males	Females
Vital capacity in millilitres. . ..	$(27{\cdot}63-0{\cdot}112Y)H$	$(21{\cdot}78-0{\cdot}101Y)H$
Maximum breathing capacity (supine) in litres per minute	$\frac{96A}{100}(86{\cdot}5-0{\cdot}522Y)$	$\frac{96A}{100}(71{\cdot}3-0{\cdot}474Y)$

[1] Y, age in years; H, height in centimetres; A, body surface area in square metres.

The estimates of residual capacity in the female group of Hurtado *et alii* appear to be disproportionately high in relation to the vital capacity. This is reflected in the figure for the residual capacity expressed as a percentage of the total capacity, the normal value being 20·0% (Baldwin *et alii*, 1948) for this age. The t test for consistency shows that there is less than one chance in 100,000 that the observed value of t would be exceeded. It is thus concluded that the value for this group is significantly higher than normal.

The source of this discrepancy is apparent from the figures for the resting ventilation per unit area of body surface, which show that these subjects as a group were hyperventilating. This would lead to an increase in the volume of nitrogen eliminated from the blood during the residual capacity determination, and therefore to an over-estimate of this capacity.

In the present series, the figures for resting ventilation per unit area of body surface in both sexes are consistent with those of Richards (1948), which have been accepted as provisional normal standards by Comroe (1951).

A possible contributing factor to minor differences between corresponding values for different groups in Table I is the slighter build on the average of Richards's subjects. Also, since the other groups comprised chiefly medical students and trainee nurses, a more competitive atmosphere was likely to be achieved than in Richards's series of hospital patients.

Estimations of the mean resting alveolar ventilation have been tabulated (Table III). As was recommended by Comroe (1951), these were calculated from resting total ventilation figures and assumed values for dead space. The latter were taken as 26% of tidal volumes, after Rahn (1950) and Fowler (1948). Thus the individual values, the mean and the standard deviation for the alveolar ventilation were obtained by multiplying the corresponding figures for total ventilation by the factor 0·74.

Index of Intrapulmonary Mixing

From the 20 subjects, 33 estimations of the index of intrapulmonary mixing were made. Of these, 17 consecutive results were significantly higher than the remainder (by the t test), and this was proved to have been caused by a very small contamination of alveolar gas with air during sampling. The mean value of the 16 reliable estimates from nine subjects was 0·58, with standard deviation 0·08 and range 0·42 to 0·76. Further discussion of the index will be included with the analysis of the open circuit technique.

TABLE III

Estimated Resting Alveolar Ventilation in Litres at B.T.P.S. per Minute per Square Metre of Body Surface Area

Observer	Number of Subjects	Males			Females		
		Mean	Standard Deviation	Range	Mean	Standard Deviation	Range
Present series	10	2·6	0·4	2·0–3·0	2·5	0·2	2·1–2·8
Richards	17	2·7	0·2	2·3–3·3	2·4	0·3	1·9–3·2

SUMMARY AND CONCLUSIONS

Selected tests of pulmonary ventilation and gas distribution have been carried out on 20 healthy male and female subjects aged twenty to thirty-five years.

Data for the same age group from various observers are tabulated for comparison. General agreement among corresponding figures is noted, and obvious discrepancies are discussed.

It is believed that this series includes (i) the first reported values for residual capacity and its derivatives in a limited age group of female subjects, obtained with adequate control of external influencing factors, and (ii) the first reported systematic study of pulmonary function in a series of Australian subjects.

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THE PROGNOSIS OF MYOCARDIAL INFARCTION WITH SPECIAL REFERENCE TO ELECTROCARDIOGRAPHIC FACTORS[1]

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THE prognosis of myocardial infarction in the acute attack is usually estimated by considering such factors as the age of the patient, previous occurrence of infarction, the duration of pain, the degree of shock, signs of cardiac failure, persistent gallop rhythm, enlargement of the heart and the presence of arrhythmias or anomalies of conduction. All except the first two of these appear to depend primarily on the size of the infarct or its situation, and with the use of multiple unipolar electrocardiographic leads it should be possible to obtain an estimate, albeit not a precise one, of this. Yet, curiously, there is no published work on this subject. The present study represents an attempt to correlate electrocardiographic evidence of the extent and situation of the infarcted muscle with the immediate prognosis.

MATERIAL

A review was made of the records of 200 consecutive patients with cardiac infarction admitted to the Royal Prince Alfred Hospital between September, 1949, and June, 1953. Several patients were admitted more than once with recurring attacks, but were treated for statistical purposes as separate patients on each admission. The only patients included were those who had autopsy or conclusive electrocardiographic evidence of cardiac infarction. The three standard, three unipolar limb and six unipolar chest leads were taken. In all except three instances conclusive electrocardiographic evidence was regarded as being the presence of abnormal Q waves; that is, (i) a Q wave 0·04 second or more in width, (ii) Q waves appearing or increasing in depth after an episode of chest pain, (iii) Q/R ratio decreasing from right to left across the precordial leads, or (iv) small Q waves preceding an rS complex in V2, V3 or V4. In aVF the criteria for an abnormal Q wave were also taken to include a Q wave with an amplitude 60% or more of that of R_{aVF}, and the same standards were applied to Q_{aVL} provided that P_{aVL} was upright (Goldberger, 1949). The three exceptions were patients admitted to hospital before the full six precordial leads were taken as routine; they had typical histories and clinical and laboratory findings, with classical S-T segment and T wave changes in the limited number of precordial leads taken. It was assumed that if six precordial leads had been taken, abnormal Q waves would have been found.

TABLE I

The Age Distribution and Mortality Rate in 200 Cases of Recent Cardiac Infarction

Age Group (Years)	Number of Cases	Deaths	Percentage Mortality	Standard Error
Under 45 ..	19	1	5	5·0
45 to 49 ..	19	4	21	9·4
50 to 54 ..	20	6	30	10·2
55 to 59 ..	43	15	35	7·3
60 to 64 ..	48	16	33	6·8
65 to 69 ..	28	11	39	9·2
Over 69 ..	23	14	61	10·2
Total ..	200	67	33·5	3·3
Total under 70	177	53	30	3·5

The series consisted of 39 females and 161 males, and the average age was 58·5 years. The age distribution and mortality in each age group are shown in Table I.

Of the 200 patients, 20 died before electrocardiograms could be taken, leaving 180 for whom one or more tracings were available. In 14 of these cases the full 12 leads were not available.

RESULTS

The overall mortality was 33·5% and the mortality rate was 25% in the patients who survived long enough to have electrocardiograms taken. The death rate was 31% in 42 patients who had a history suggestive of previous cardiac infarction.

[1] Received on October 9, 1954.

TABLE II

Observation	Group I			Group II Anterior, Severe	Group III Both Surfaces	Total
	Anterior	Posterior	Total			
Number of cases	55	49	104	29	47	180
Deaths	9	4	13	9	23	45
Percentage mortality	16	8	12·5	31	49	25
Standard error	4·9	3·9	3·2	8·6	7·3	3·2

Electrocardiographic Data

The cases were divided into three groups on the basis of the extent of the abnormal *Q* wave distribution. Group I consists of patients with electrocardiograms in which the *Q* wave was present only in aVL or aVF, or in three or less of the precordial leads. In Group II the *Q* waves occur in four or more of the precordial leads, but not in aVF. In Group III *Q* waves are present in aVF and also in the precordial leads; also included in this group are eight cases in which there was an abnormal *Q* wave in aVF, with deep inverted *T* waves but no *Q* wave in the precordial leads. It was considered that these *T* waves were sufficiently indicative of severe impairment of the coronary supply to the anterior myocardium to warrant inclusion of such cases in this group.

TABLE III

The Incidence and Mortality Rate of the Arrhythmias and Conduction Defects, and the Relationship to the Site of Infarction

Arrhythmia	Number of Cases	Number of Deaths	Location of Infarct
Auricular fibrillation	8	5	5 anterior, 2 posterior, 1 combined
Auricular tachycardia	2	1	1 anterior, 1 posterior
Nodal tachycardia	1	1	Combined anterior and posterior
Ventricular tachycardia	2	1	2 posterior
Paroxysmal tachycardia of undetermined origin	3	2	1 anterior, 1 posterior, 1 combined
Auriculo-ventricular block, first and second degree	5	2	3 anterior, 1 posterior, 1 combined
Complete heart block	2	2	1 posterior, 1 combined
Left bundle branch block	3	2	2 anterior, 1 posterior
Right bundle branch block	13	8	8 anterior, 2 posterior, 3 combined
Delayed intraventricular conduction, indeterminate type	3	2	1 posterior, 2 combined
Total number of abnormalities	42	—	Total number of anterior infarcts, 20
Total number of cases	37	22	Total number of posterior infarcts, 12

The number and mortality rate in each group are shown in Table II. The difference between Groups I and III is highly significant statistically, but owing to the small number of cases in Group II no conclusion can be drawn from the figures for this group.

A comparison of the prognosis of pure posterior and pure anterior infarcts, those in which there was electrocardiographic evidence of involvement of both surfaces being omitted, revealed that there were 18 deaths in 84 cases of anterior infarction (21%), and only four deaths in 49 cases of posterior infarction (8%).

Of the 180 patients, 12 showed electrocardiographic evidence of arrhythmia and 25 of conduction defect. Among these 37 there were 22 deaths giving a mortality rate of 59%, which was approximately equal in both series. Details are shown in Table III.

DISCUSSION

The criteria for the diagnosis in this series will have excluded a certain number of patients with small infarcts which did not lead to the production of a *Q* wave in the electrocardiogram. From the studies of East and Oram (1948) and of Papp and Shirley Smith (1951), it would appear that the prognosis in cases of infarction without *Q* waves is very good, so that the omission of these from the series will not give a falsely low mortality rate in Group I. If the findings of Prinzmetal *et alii* (1953) are confirmed, patients with infarction involving only the subendocardial portion of the ventricular wall will also have been excluded. However, in this series, of the 28 patients for whom both electrocardiographic and post-mortem findings were available, only two were found to have infarcts which had not produced *Q* waves. The first of these had a small infarct in the basal portion of the anterior ventricular wall, and the electrocardiogram showed only a depressed *S-T* segment and inverted *T* wave of the "left ventricular strain" type in the precordial leads. The second had *S-T* segment elevation in V2, V3 and V4; but unfortunately the autopsy report did not specify the exact distribution of the infarcted areas in the ventricular wall, and so the question whether this was an example of subendocardial or subepicardial infarct cannot be answered.

However, certainly there was not more than one possible subendocardial infarct in these 28 cases. The inference is that this type of infarct occurs infrequently or that it is rarely fatal. Papp and Smith (1951), out of a total of 109 cases of suspected infarction, described 23 with *T* wave changes in the absence of what they call " pathological *Q* waves ", and assumed that in these cases the infarct was intramural. This suggests a high incidence of intramural infarction; but they may have been overstringent in their criteria of pathological *Q* waves, as the electrocardiogram in their Case I, classified as without abnormal *Q* waves, shows the development of a definite *Q* wave in V3 and splintering in V2 following a previously normal tracing. It is possible that other similar electrocardiograms in their series would reduce the number of infarcts classifiable as truly intramural by Prinzmetal's standards.

Myers *et alii* (1948), in their extensive correlation of electrocardiographic and post-mortem findings, described only two cases out of 50 in which the infarct was intramural in the anterior wall of the ventricle, and in which no *Q* wave was demonstrated in the precordial leads.

Experience at the Hallstrom Institute during a twelve months' period has been that amongst 98 consecutive patients with a diagnosis of myocardial infarction, six had *T* wave changes in the absence of abnormal *Q* waves, an incidence of 6·1%. In all six, as well as the electrocardiographic changes there was either fever, leucocytosis or a raised erythrocyte sedimentation rate to indicate necrosis. In this group there was only one death, and that was a death in coma following an overdose of dicumarol. No autopsy was performed; but it does not seem justifiable to attribute this death directly to cardiac infarction. There is no pathological proof of the location of the infarct in these cases; but in the light of Prinzmetal's findings it could be argued that subendocardial infarcts were present, and that the inverted *T* waves represent a zone of altered repolarization in the subepicardial muscle due to relative ischæmia (Bayley, 1942). Prinzmetal does not record the *T* wave findings in his series; but in one of his illustrative electrocardiograms of subendocardial infarction inverted *T* waves are shown.

From the available evidence it seems probable that pure subendocardial infarction is not common and is rarely fatal.

As was shown in Table I, the prognosis is greatly altered by increasing age of these patients; in patients aged over sixty-nine years the mortality rate is 61%—that is, about twice that of the younger age groups. When age is related to the extent of the infarct, the average ages for the groups in Table II are as follows: Group I, fifty-seven years (10); Group II, sixty-two years (six); Group III, 60·5 years (seven). (The numbers in parentheses indicate the number of patients over the age of sixty-nine years in each group.) It is apparent, therefore, that age plays little part in determining the difference in mortality between the groups.

Despite reports by various observers (Woods and Barnes, 1942; Master *et alii*, 1937) that a history of previous infarction makes for a worse prognosis, in the present series as in that of Rathe (1942) and Linden (1952) the prognosis was unchanged by a history of previous infarction. The death rate among patients with a history suggestive of previous infarction was 31% as compared with the overall mortality of 33·5%, so that this factor cannot be relevant to the differences in Groups I, II and III. At first sight this is surprising, as it would appear that a myocardium with one segment fibrosed would have less reserve than a previously normal ventricle. However, Murray (1947) has produced evidence from experiments on the hearts of dogs that one of the major factors in the loss of mechanical efficiency following infarction is the aneurysmal bulging of the toneless infarcted muscle during each systole. On the other hand, fibrotic scar tissue, though non-contractile, is sufficiently strong to resist stretching in most cases, and its presence does not appear to affect cardiac function seriously, as is evidenced by the good exercise tolerance of large numbers of patients after recovery from cardiac infarction. There is therefore no reason why a heart with a small area of scarring should fare any worse in the event of a new infarct than one previously unaffected, provided that the extent of the recent involvement is the same in both cases.

The results show that the occurrence of arrhythmias and conduction defects leads to a worse prognosis, as has been pointed out by Woods and Barnes (1942) and by Askey and Neurath (1945). However, in Group I, only seven out of 18 patients with these complications died, while in Group II there were five deaths in six cases and in Group III, nine deaths in 12 cases. In other words, the size of the infarct is still a significant factor in determining the outcome even in the presence of other serious complications. There is a striking preponderance of electrocardiograms

showing right bundle branch block, most of them being associated with anterior infarction. However, this may be purely a chance finding due to the small samples taken. As shown in Table III, there was no apparent relationship between the site of the infarct and the occurrence of conduction defects or arrhythmias when the 2 : 1 ratio of anterior to posterior lesions in the total series is taken into account. Neither was there any correlation between the size of the infarcts and the occurrence of these abnormalities.

The findings regarding prognosis of anterior and posterior infarcts are not in accord with those of Master *et alii* (1936), of Woods and Barnes (1942), of Mintz and Katz (1947), of Linden (1952) or of Smith (1953). However, in some of these multiple precordial leads were not taken. Under these circumstances a number of localized changes in the precordial leads will have been missed, and it is these changes which in the present series placed the patient in Group III (the combined antero-posterior group). The result would have been to load the group of posterior infarctions in the foregoing series with infarcts which are actually antero-posterior and thus have a much worse prognosis. Jacobs (1951) and Littman (1949) have found figures for posterior infarction comparable to those in the present group, but both with small series. In the present series the anterior group may include cases in which actually both surfaces of the ventricle are affected, but because of the wide projection of the aVF lead onto the posterior surface of the heart, minor localized changes in electrical potential are submerged in the surrounding normal electrical phenomena, and so electrocardiographic evidence of minor changes in the posterior wall is lacking. On anatomical and pathological grounds there seems to be no reason why infarctions of the anterior and posterior walls should differ in mortality rates, particularly as there has never been any good evidence to relate particular complications to the situation of the infarct. It seems much more likely that the differences observed have been due to inadvertent loading of one of those categories with antero-posterior infarcts. Earlier reports, before multiple precordial leads were taken as a routine procedure, tended to show an equal mortality rate for the two groups, whereas more recent figures, eliminating the posterior infarct with slight anterior involvement, give the very low mortality rate of under 10% for the pure posterior infarct. It seems possible that, if the same separation could be made for anterior infarctions, the mortality of pure anterior infarction would be shown to be similarly low.

The significance of even slight damage to the second surface of the ventricle is presumably due to the restriction of adequate collateral supply when two main coronary branches are grossly diseased. The serious prognosis associated with septal infarction (Littman, 1949) appears also to be dependent on the fact that two main coronary artery branches are affected by severe atheroma or thrombosis. In Littman's series of 11 fatal cases of septal infarction, nine showed evidence of blockage of two coronary arteries, in one extensive atheroma was present and in the other only gross anæmia was found.

The foregoing observations suggest that in the prognosis of a case of cardiac infarction the most important single factor is the extent of the infarcted muscle as indicated by the electrocardiogram. The advantages of a purely objective criterion of prognosis are obvious.

SUMMARY

Cardiac infarcts in 180 patients are classified into three groups depending on the extent of the abnormal *Q* waves in the twelve-lead electrocardiogram.

It is shown that the prognosis is related to the size of the infarct as estimated in this way, independently of other variables. When the electrocardiogram indicated involvement of two surfaces of the heart, the mortality rate was 49%. When *Q* wave changes were limited to the posterior surface of the heart or to three or less precordial leads, the mortality rate was 12·5%. Where four or more precordial leads showed abnormal *Q* waves, the mortality rate was 31%.

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ADDENDUM

Since this article was written an exhaustive review of the subject and a study of 127 cases has been published by Josef Burstein in *Acta medica scandinavica*, Supplement 285. Amongst other findings Burstein reached similar conclusions to those presented in this paper on the value of electrocardiographic data in determining the prognosis of cardiac infarction.

CONTROL OF BODY WATER CONTENT : A STUDY OF DAY-TO-DAY VARIATIONS IN HUMANS AND RABBITS[1]

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IN studies of water balance, as with any other form of clinical measurement, it is important to recognize a normal range of variation and to try to describe its limits. A diurnal rhythm of variation in body water content is well recognized (Manchester, 1933 ; Borst and de Vries, 1950), but little is known about day-to-day fluctuations.

According to Dodds (1950), the body weight of normal people varies by no more than 0·45 kilogram from day to day ; but his main interest was in obesity, and he gave no details of the water exchanges of his experimental subjects. However, Lowe (1951) has published the daily water balance curves of two patients with unrestricted fluid intake who were each in a " steady state " of body water content for a period of three weeks. Both showed a range of variation of about ±500 millilitres, and this observation suggested the need for a more detailed study of these daily fluctuations.

Adolph (1943) reviewed the few other long-term studies of water balance which have as yet been made in mammals : 15 observations in one rabbit (Gompel, Hamon and Mayer, 1936) ; 42 in one cat (Gasnier and Mayer, 1937) and 80 in one rabbit (Gasnier and Mayer, 1939) ; 18 pooled observations from four healthy humans (Adolph and Dill, 1938) ; 27 observations in one dog and 10 in each of two rats (Adolph, 1943). However, Adolph did not give the ranges of the variations found, but only their standard differences, and unfortunately the studies of the other workers were unavailable to me.

For this present work it seemed that both the maximum difference and the standard difference were needed to give the best numerical description of any day-to-day variations in body water content. In this paper both parameters will be presented for 303 daily observations on 12 humans and for 164 observations on six rabbits.

[1] Received on October 8, 1954.

[2] Victor Y. and Margaret Kimpton Research Scholar, 1954.

SUBJECTS AND METHODS

To conduct such a long-term study on perfectly healthy people, although theoretically desirable, would be a great administrative problem, and so the human observations reported here were made in retrospect on selected ward patients. These observations were complemented by an elective study on healthy rabbits which were readily available and convenient for the purpose.

Humans

Daily water balances have now been measured in a wide variety of the patients admitted to the clinical research ward during the past few years. The details of this procedure and the errors involved have been fully discussed elsewhere (Lowe, 1951). Twelve such patients were selected for study according to the following criteria : there was no obvious upset of their fluid balance, the period of study was at least two weeks, and the daily weight records were complete.

TABLE I

Features of the " Normal " Human Group[1]

Diagnosis	Number of Patients
Essential hypertension ..	5
Recent congestive cardiac failure	3
Osteomalacia	1
Alcoholism	1
Addison's disease	1
Renal acidosis	1
Total	12

[1] Five male subjects, seven females ; age, twenty-nine to eighty-two years ; weight, 40 to 80 kilograms ; period of observation, thirteen to forty-nine days.

The overall composition of this selected " normal " group is shown in Table I.

Rabbits

Six healthy adult cross-bred rabbits, ranging in weight from 2·2 to 2·8 kilograms, were studied for periods of from three to five weeks

while in a " steady state " of water content. They were confined to metabolism cages and allowed whatever quantities they chose of dry food pellets[1] and, with one exception, of water.

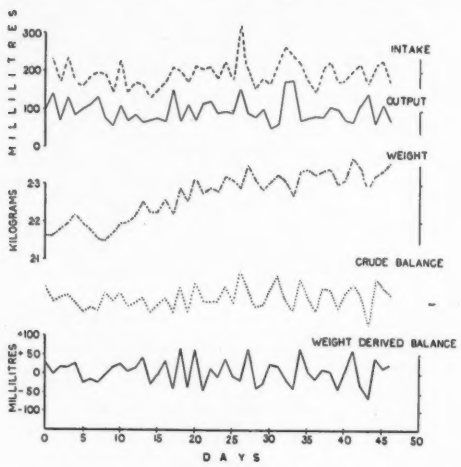

FIGURE I

Rabbit C: Typical variations of intake, output, body weight and water balance of a healthy rabbit under standard conditions. The crude balance curve, which is the oral intake *minus* the urinary output, is plotted on the same scale as the others, but with an arbitrary origin, because no correction was made for gain or loss by other routes. The weight derived balance is a curve of the daily weight changes. (Only the last five weeks were included in the present study)

For one rabbit the water intake was fixed at 200 millilitres per day. Such a régime, with no fresh greens at all, will maintain the weight, health and fertility of rabbits over several generations (Bruce, 1947). Their intake of water, output of urine and body weight were measured every twenty-four hours and charted as in Figure I, which shows the typical performance of a normal rabbit under these standard conditions.

The error of weighing was not more than 0·25%, but the volumetric error was usually of the order of 5%.

The daily weight changes were not significantly affected by variations in bladder urine. The rabbits seldom passed urine more often than once or twice in a day, so that, before they were weighed, any retained urine was easily detected and expressed by hand.

As the weights are always more accurate than the crude fluid balance measurements, the daily weight changes were taken to be predominantly changes in body water content and to be the best available estimate of the water balance. This assumption seems justified for rabbits under these particular conditions of study, since there is a very close resemblance between the crude fluid balances and those derived from the weights (Figure I). The assumption is also valid for patients under the ward conditions of study, as can be shown by superimposing their weight-derived balance curves on the observed fluid balance curves (Lowe, 1952).

OBSERVATIONS

In two rabbits (B and C, Table III) there was a slow steady weight rise during the period of study (Figure I), but in the others there was no significant weight trend. However, the derived water balance curve (Figure I), representing

[1] " Barastoc " Products, Number 9, made by W. S. Kimpton and Sons, 395 Collins Street, Melbourne.

TABLE II

Variations in Body Weight of 12 Patients in Water Balance for from Two to Seven Weeks

Patient	Sex	Age (Years)	Diagnosis	Days	Median Body Weight (Kilograms)	Weight Range (Kilograms)	Daily Weight Changes (Grammes)	
							Maximum	Standard Difference
V.K. ..	M.	39	Essential hypertension	19	71·20	1·0	525	203
L.D. ..	M.	58	Recent congestive cardiac failure	16	56·45	0·7	500	170
G.M. ..	M.	52	Essential hypertension	15	55·65	0·7	525	192
J.R. ..	M.	29	Osteomalacia	38	64·70	1·2	725	234
F.P. ..	M.	82	Recent congestive cardiac failure	30	58·00	3·0	650	235
E.S. ..	F.	43	Addison's disease	28	44·70	2·2	700	223
L.N. ..	F.	43	Chronic alcoholism	24	41·20	1·3	600	223
M.P. ..	F.	59	Recent congestive cardiac failure	22	40·40	1·2	500	169
H.F. ..	F.	54	Renal acidosis	49	52·65	1·7	700	212
K.McN. ..	F.	54	Essential hypertension	25	55·15	0·9	550	189
B.P. ..	F.	29	Essential hypertension	13	68·05	1·5	475	200
T.B. ..	F.	47	Essential hypertension	24	80·65	1·7	500	216
Total ..	..	..	.. ..	303	—	—	—	—

the daily weight changes, ignores trend and emphasizes only the fluctuations of water content.

The statistical correlation between the weight-derived and crude water balance curves was calculated both for one rabbit with a positive

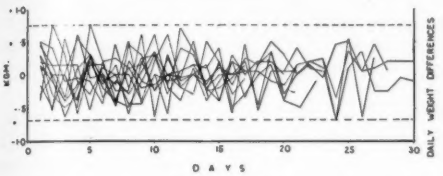

FIGURE II

The daily weight differences of 12 patients in fluid balance, superimposed to show what variations can occur, and in particular, their range.

weight trend, and for one other with no trend, with the following results:

Rabbit B (positive trend): $N=35$; $r=0\cdot80$; $t=7\cdot7$ (33 *d.f.*); $P<0\cdot001$.

Rabbit E (no trend): $N=30$; $r=0\cdot82$; $t=7\cdot6$ (28 *d.f.*); $P<0\cdot001$.

These are very highly significant correlations, and they lend additional support to the validity of this method of study.

TABLE III

Variations in Body Weight of Six Rabbits in Water Balance for from Three to Five Weeks

Rabbit	Number of Observations	Median Body Weight (Grammes)	Weight Range (Grammes)	Daily Weight Changes (Grammes)	
				Maximum	Standard Difference
A	25	2860	115	55	19·3
B	36	2330	410	55	23·1
C	33	2295	220	55	26·6
D	21	2250	175	72·5	29·8
E	29	2195	180	55	22·0
F	20	2460	100	42·5	17·1
Total	164	—	—	—	—

The following observations, then, are concerned mainly with daily weight changes.

The curves of the patients' daily weight changes are superimposed (Figure II) to give some idea of the fluctuations of body water content which can occur in humans and to show that their range is $\pm0\cdot75$ kilogram or litre.

The accompanying tables summarize the observations on the individual patients (Table II) and on each rabbit (Table III).

The standard difference was calculated as $1/\sqrt{2}$ times the root mean square of the daily weight differences (Adolph, 1943), and in a large sample should include two-thirds of the observations. However, for purposes of comparison, both the maximum difference and the standard difference of the daily weight changes, expressed as percentages of body weight, give the most useful numerical description of the data (Tables IV and V).

TABLE IV

Daily Weight Changes: 303 Observations on 12 Patients

Patient	Percentage of Median Body Weight	
	Maximum	Standard Difference
V.K.[1]	0·74	±0·29
L.D.	0·89	0·30
G.M.	0·94	0·35
J.R.	1·12	0·36
F.P.	1·12	0·41
E.S.	1·57	0·50
L.N.	1·46	0·54
M.P.	1·24	0·42
H.F.	1·33	0·40
K.McN.	1·00	0·34
B.P.	0·70	0·29
T.B.	0·62	0·27
Range	0·62 to 1·57	±0·27 to ±0·54
Mean	1·06	±0·37

[1] Constant intake of two litres per day.

TABLE V

Daily Weight Changes: 164 Observations on Six Rabbits

Rabbit	Percentage of Median Body Weight	
	Maximum	Standard Difference
A[1]	1·92	±0·67
B	2·36	0·99
C	2·40	1·16
D	3·22	1·32
E	2·51	1·00
F	1·73	0·70
Range	1·73 to 3·22	±0·70 to ±1·32
Mean	2·36	±0·97

[1] Fixed intake of 200 millilitres per day.

All the patients were allowed whatever fluid intake they chose, but nevertheless one patient (V.K.) maintained a constant intake of two litres per day. In spite of this his weight varied as much as that of some of the other patients, and similarly the one rabbit with a fixed intake (Table V) had a variation almost as great as those of its fellows.

The two parameters for man and the rabbit are contrasted in Table VI.

The cyclical fluctuations in body water content are often so regular (Figure I) as to suggest some underlying rhythm in the water balance over and above the already well-known

TABLE VI

Daily Weight Changes: Species Difference

Species	Percentage of Median Body Weight			
	Maximum		Standard Difference	
	Mean	Range	Mean	Range
Rabbit ..	2·36	1·73 to 3·22	±0·97	±0·70 to ±1·32
Man ..	1·06	0·62 to 1·57	±0·37	±0·27 to ±0·54

diurnal rhythm. Adolph (1943) investigated this possibility in the one dog he studied. Similar tests of randomness were applied to the observations on Rabbit C of this series, and the results (Table VII), showing that the variations are in fact random, are in agreement with those of Adolph.

TABLE VII

Random Nature of Cyclical Variations in Body Water Content

Test	Expected Values for Random Series	Observed Values (Rabbit C)
Average number of points succeeding in one direction (a run) ..	2·5	2·4
Number of points in two succeeding runs (a gap)	4	3·81
Percentage of points moving towards trend (here line of zero balance)	75	68·75

DISCUSSION

In spite of the diversity of age, weight and disease, there is sufficient uniformity of regulation within the group of patients studied (Figure II and Table IV) to assume that the body water content of normal people would have a variation similar to that of this group.

It is possible that greater fluctuations might occur during the menstrual cycle, since only three women of menstrual age were included in this study. Thomas (1953) records an extreme range of fluctuation of ±2·85% of mean body weight in one apparently healthy girl student, but the majority of her subjects varied within a range of ±1·0% to ±1·8% during their menstrual cycles. This is similar to the range found by Danforth, Boyer and Graff (1946) and is only slightly above the range found in this present study.

The rabbits' water turnover, relative to body weight, was roughly two or three times that of the patients, and it is interesting that the comparative figures for daily variations in the rabbit are twice to three times those for man (Table VI). In other words, the greater the relative turnover, the greater is the opportunity for variation.

This probably explains why the present figures for the standard difference in the rabbit are somewhat lower than those of 1·53 for the rabbit of Gompel, Hamon and Mayer (1936), or 1·49 for the rabbit of Gasnier and Mayer (1939), both of which rabbits were fed on cabbage. In my experience the water turnover in rabbits fed on cabbage is higher than in those given dry food.

The results in the patient and in the rabbit who had constant water intakes (Tables IV and V) suggest that variation of intake is not the major source of these long-term fluctuations in total body water.

Edelman *et alii* (1952) measuring total body water by the deuterium oxide dilution technique, tested the reproducibility of their method in six healthy subjects by two estimates at intervals of from seven to 155 days. It is interesting to consider the differences between each first and second estimate, expressed as a percentage of body weight. The mean difference was only 0·7%, the differences in five subjects ranged from 0·1% to 1·2%, and only one, with a difference of 1·9%, lay outside the range of fluctuations found in this present study (Table IV). Although these differences might well have been due to overall experimental error, they could equally well have been due to random fluctuations of water content.

These fluctuations, then, should be taken into account in any measurements of total body water, or for that matter of any of its compartments, since one might expect that these could be affected in a similar proportion.

SUMMARY

The daily weights and water balances of 12 selected ward patients and of six normal rabbits have been studied under defined standard conditions.

Daily weight changes have been shown to be the best available estimate of changes in body water content.

A statistical analysis of these daily weight changes is presented in an attempt to describe "normal" ranges of variation.

From day to day there are normal, random, limited variations in body water content, which are cyclical but not rhythmical.

The significance of these variations in total body water is discussed.

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AN UNEXPECTED SLOW PHASE IN THE EQUILIBRATION OF BODY WATER CONTENT[1]

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THE regulation of body water content over short periods has already been well studied, more especially after the withdrawal or the giving of water, and it seems by all accounts that water, physiologically, is one of the most rapidly equilibrating substances known.

The results of many of these short-term experiments have been brought together by Adolph (1943) to show that there is a general biological pattern of early recovery of balance from positive or negative water loads. Depending on the animal species and the type of water load, this early phase lasts several minutes, or at the most a few hours, during which there is an almost exact return to the original water content. Even when water deprivation for four or five days is the load employed, the subsequent equilibration is remarkably swift if water is freely available.

Moreover, it has been found that this initial equilibrium then persists for several hours, and so there has been little reason to suppose that such upsets would have any long-term effects on water balance. In fact, two of the long-term responses found in this present study (Figure I) might have been expected, since they conform to the pattern of recovery found by other workers in their short-term experiments.

However, the first clue to a different sort of behaviour was the observation by Lowe (1951) that in œdematous patients returning to normal there were large oscillations in their body water content which might take many days to subside. Only then was it obvious that even for normal water balance, or its recovery from various types of load, there was very little long-term information available.

A long-term study of the fluctuations of normal water balance in humans and rabbits (Fowler, 1955) forms the background for this present work, which shows that a rather prolonged recovery phase can follow some moderate disturbance of water balance. The features of this phase are large fluctuations of body water content, subsiding only after several days to the range of fluctuation which is characteristic of normal.

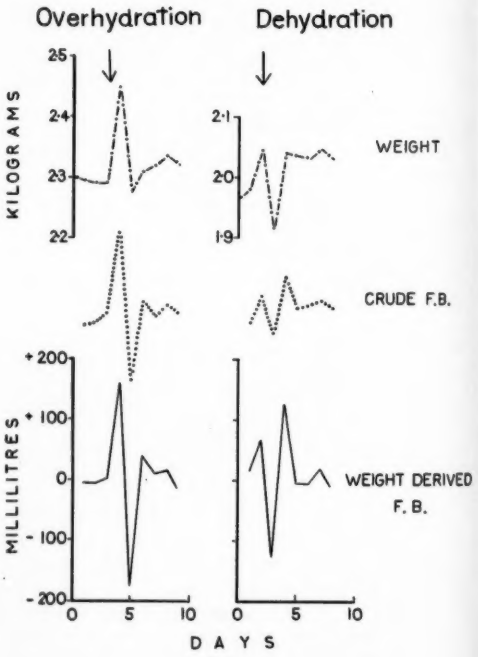

FIGURE I

Two examples, from rabbits, of rapid equilibration of body water content after overhydration (Rabbit 25) and dehydration (Rabbit 29). Notice that a single deflection and recovery in the weight curves is accompanied by a biphasic response in the fluid balance curves. (Compare with Figures V and VI)

Already the water balance curves of several non-œdematous patients have shown, after short disturbances, this general pattern of slow recovery. However, since no deliberate interference has as yet been tried in humans, the

[1] Received on December 9, 1954.

[2] Victor Y. and Margaret Kimpton Research Scholar, 1954.

observations presented here are mainly the results of interference with water balance in rabbits.

It is hoped that the close analogy between these experimental findings and the human observations will draw attention to a phenomenon which is not only of general physiological importance but also of clinical interest. It seems that up till now this slow phase in the equilibration of total body water content has not been recognized as a normal response of the mechanisms controlling body water volume.

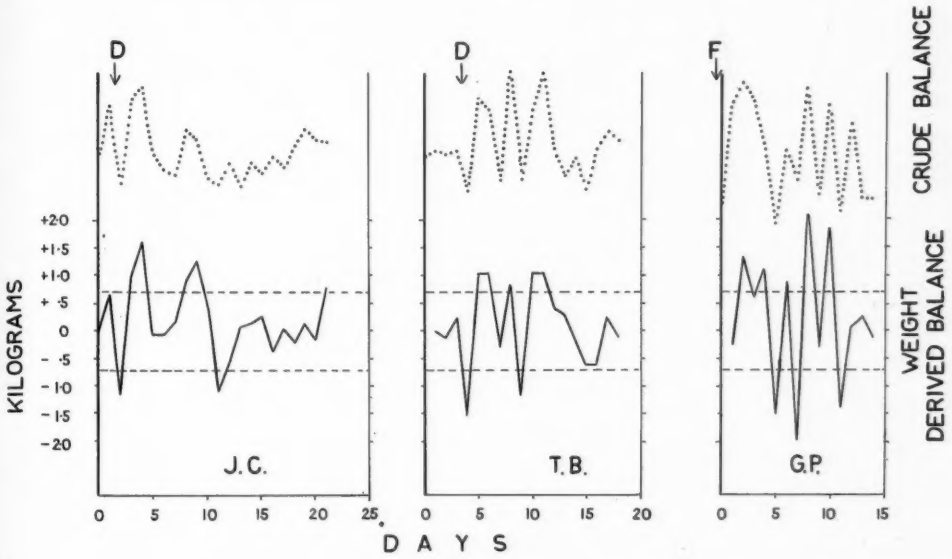

FIGURE II

Water balance curves of three patients with slow recovery from the brief disturbances indicated; D signifies dehydration, and F, fever

PROCEDURES

The three patients whose clinical details are reported here were free to choose their own water intake, and their daily water balances were studied by a method which has already been described in detail (Lowe, 1951).

Healthy adult rabbits were confined to metabolism cages and allowed whatever quantities they chose of dry food pellets and, in most experiments, of water. However, in a few experiments, as will be indicated, a maximum intake of water was fixed at a level a little above that needed to keep an undisturbed rabbit in water balance.

Rabbits 1 and 2 at first received their only water supply as fresh green cabbage daily. Since this usually has a water content of about 90% to 95%, the weight of cabbage eaten each day was taken, without correction, as the water intake for that period. In spite of this approximation there was still quite a satisfactory correlation between the crude and weight-derived water balance curves (Figures IIIA and IVA). Instead of cabbage, water-bulbs of conventional design (Wilson, 1947) were later used to supply these two with their drinking water, but were finally discarded because of certain practical disadvantages inherent in this type of vessel, and because of its limitation of the greatest possible intake (Lane-Petter, 1952).

Later on, when it was desired to study the balance patterns of animals entirely free to regulate their own water intake, a drinking-can was adopted which is similar in principle and design to one described recently by Lazarow (1954).

All the rabbits then, except Rabbits 1 and 2, received water *ad libitum* both before and after each disturbance.

In both patients and rabbits the intake of water, the output of urine and the body weight were measured every twenty-four hours, and from these the crude water balance and weight-derived water balance curves were drawn.

The crude water balance is simply the measurable oral intake *minus* the urinary output. It is plotted on the same scale as the

other curves, but with an arbitrary origin, since no correction is made for insensible water gains and losses.

The weight-derived balance curves consist of the daily weight changes, which are assumed to be predominantly changes in body water content. Over long periods, and under the stated standard conditions of study, this assumption has been justified by correlating the crude and the weight-derived balance curves—graphically for patients (Lowe, 1952), and both graphically and numerically for rabbits (Fowler, 1955).

As the weights are always far more accurate than the crude fluid balance measurements, the weight-derived balance curve is to be preferred as the best available estimate of water balance. The following demonstrations of a slow recovery phase are therefore based on the weight-derived balance curves.

However, it had to be shown that there was still a satisfactory correlation between the two types of balance curve during the shorter periods of recovery from various upsets of water balance. Both curves, therefore, are pictured here for the three patients (Figure II) and for a convincing number of responses in the rabbits (Figures I, III, IV, V and VI).

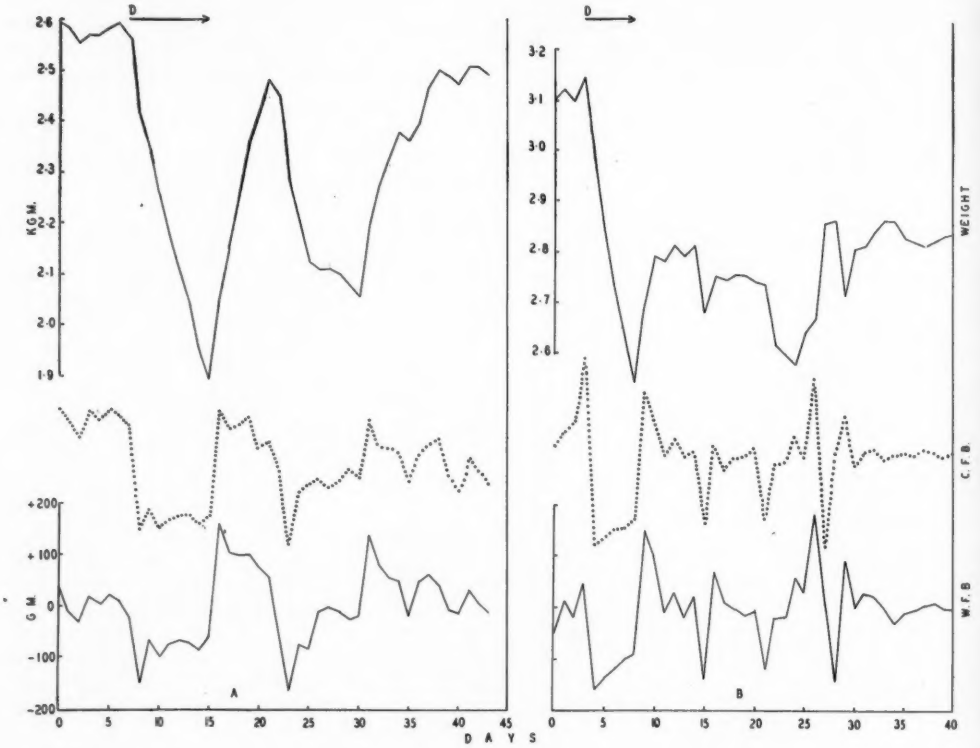

FIGURE III

Prolonged excessive fluctuations of body water content, despite fixed intakes, during recovery of rabbits from water deprivation (D): for eight days in A (Rabbit 2) and for five days in B (Rabbit 1). In this and all the subsequent figures C.F.B. stands for crude fluid balance and W.F.B. for weight-derived fluid balance

In only one patient (T.B.) was there a satisfactory control period prior to the disturbance. However, each rabbit could be used as its own control, because its water balance was studied for at least four or five days before any interference was made. To help in defining some of the recovery periods, the maximum range of these basal fluctuations has been indicated by horizontal lines on the weight-derived balance charts (Figures IV, V and VI); but in most of these curves the period of excessive fluctuations will be obvious.

The remaining details of procedure, and of the various disturbances of water balance which were studied, must be described with the individual observations to which they are relevant.

OBSERVATIONS

Patients

The fluid balance curves of three non-œdematous patients are shown in Figure II and the relevant clinical details are as follows:

J.C., a man, aged sixty-three years, with essential hypertension, was admitted to the ward of the Clinical Research Unit for routine investigation. In preparation for intravenous pyelography and a renal function test, which were both performed on the same day, he was given an aperient and was then deprived of water for twelve hours. His recovery of normal water balance after this dehydration was surprisingly slow.

T.B., a man, aged twenty-nine years, with essential hypertension, was also admitted for routine investigation. He was given castor oil in preparation for intravenous pyelography and had profuse diarrhœa on the day indicated. The effects of this upset of his water balance were likewise slow to subside.

G.P., a man, aged forty-two years, felt feverish one day, and on the next had an acutely painful hip joint for which he was admitted to the ward. There his temperature was always normal and within a day or two his symptoms had subsided; but in spite of full investigation their cause was not discovered. It is interesting to see the large fluctuations in his body water content, which were only subsiding in the few days just before his discharge from hospital.

The response of the second patient is the most satisfactory of these demonstrations, because his water balance was studied for four days prior to the interference, and so a normal base line is available for comparison with what follows. However, all three patients have fluctuations far in excess of $\pm 0{\cdot}75$ kilogram, which was found to be the maximum range of variation in a group of 12 other patients in water balance (Fowler, 1955).

Rabbits

Dehydration.—Rabbit 1 was at first in water balance for six days (Figure IVA) on a fixed daily intake of 200 grammes of fresh cabbage. Then for two days this was reduced to 100 grammes per day, which was inadequate to keep this animal in balance, and it lost $4{\cdot}5\%$ of its body weight. For the next five days cabbage was allowed *ad libitum*, and thereafter was again fixed at a maximum. As judged by the prolonged excessive fluctuations of the weight and balance curves, which can easily be seen to "overswing" the equilibrium range, recovery took about ten days.

Subsequently Rabbit 1 was deprived of water for five days and lost $19{\cdot}2\%$ of its body weight (Figure IIIB). It was then given water from a 250 millilitre bulb, and as the maximum intake was thereby fixed, it seemed reasonable to expect a slow, steady return to full hydration and water balance. Instead, there were large irregular fluctuations of the weight and balance curves, which subsided only after three to four weeks.

Rabbit 2 (Figure IIIA) was originally in balance on the cabbage régime; but after water deprivation for eight days it had lost

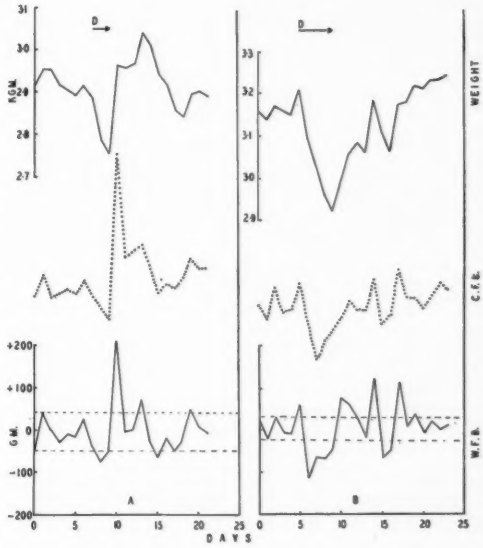

FIG 4

FIGURE IV

Slow equilibrations of body water content after partial water deprivation (D) for two days in A (Rabbit 1) and for four days in B (Rabbit 20). Water intakes were unrestricted during recovery from these and all the succeeding interferences. In the initial period of balance in A (Rabbit 1), a fixed amount of cabbage was given

$26{\cdot}3\%$ of its body weight. Then it too received its water from a 250 millilitre bulb; but after an initial steady return to somewhere near full hydration there were further large unexpected swings of the weight and balance curves. By these standards, its recovery took in all about four weeks.

Rabbit 20 had a very inadequate water intake for four days, during which it lost $9{\cdot}2\%$ of its body weight. Here again (Figure IVB) is a pattern of big oscillations with recovery taking at least ten days.

Rabbit 5 (Figure VA), Rabbit 4 (Figure VB), and Rabbit 8 (Figure VC) were all deprived of water for twenty-four hours, and although their body weights fell by only 5·7%, 4·5%

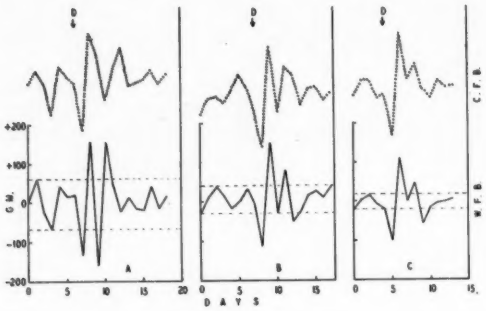

FIGURE V

The effects of water deprivation (D) for twenty-four hours in three rabbits: Rabbit 3 (A), Rabbit 5 (B), and Rabbit 8 (C). Contrast these with the single biphasic responses shown in Figure I

and 4·0% respectively, each of their recoveries can still be seen to take several days at least. By contrast, if equilibration had been rapid, a simple biphasic response of the type recorded in Figure I would have been found.

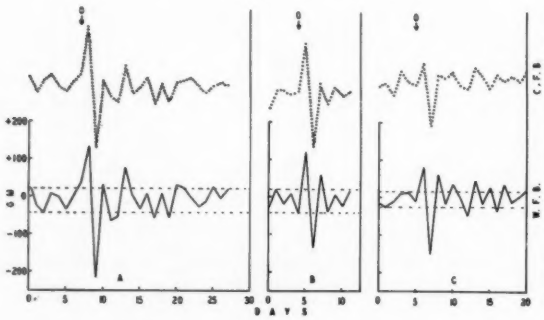

FIG. 6.

FIGURE VI

Slow equilibrations after over-hydration (O) with 5% glucose solution in Rabbit 24 (A) and with 0·9% sodium chloride solution in Rabbit 26 (B and C)

Rabbit 29, for example, after water deprivation for twenty-four hours, lost 6·3% of its body weight, but in this instance (Figure I) equilibration was rapid.

Overhydration.—Positive water loads were produced by steady infusions of isotonic fluids, given during a period of three hours into a marginal ear vein. It was intended that the size of these loads should be approximately equal to, or slightly in excess of, those negative loads which resulted from twenty-four hours of water deprivation.

Rabbit 25 provided another example of rapid equilibration (Figure I). It received sufficient of a 5% solution of glucose in water to raise its body weight by 7·0%.

However, in three other experiments a delayed recovery was found.

Rabbit 24 received a load of 5% glucose solution in water equal to 7·5% of its body weight. It is not obvious just when the recovery period was complete, but it took at the very least five days (Figure VIA).

Rabbit 26, after a load of 0·9% sodium chloride solution equal to 4·3% of its body weight, had a slightly delayed recovery phase (Figure VIB). In a later experiment 0·9% sodium chloride solution was again infused into this rabbit, and this time its body weight was raised by 6·5%. The recovery was even slower on this occasion (Figure VIC), although its exact duration is hard to state.

DISCUSSION

In both humans and rabbits, then, after relatively brief disturbances of water balance, an unexpectedly slow recovery phase can be recognized as a series of excessive fluctuations of body water content. This is the only generalization possible from the recorded data, since the individual patterns of response were very variable from patient to patient, from rabbit to rabbit, and even in the same rabbit after a repetition of the same type of load (Figure VIB and C).

In the rabbit this slow recovery can occur whether the water load is positive or negative, moderate or gross, and whether or not it creates an osmotic load; whether the water intake is free or fixed, and whether cabbage or water alone is given with the dry food.

However, rapid recovery can sometimes follow approximately equivalent degrees of loading (Figure I), although at present it is not known how to produce either a fast or a slow response at will.

As to what degree of negative loading can be tolerated, there have been very few observations up to date, and so it is interesting to note, in passing, that in Rabbits 1 and 2, after water deprivation, a loss of 20% to 25% of body weight is compatible with survival, if at the same time adequate food is available.

Certain differences between the observations in the humans and in the rabbits require further comment.

The correspondence of the two types of balance curve was even better in the rabbits than in the patients, since the error due to the water content of the rabbit's dry food pellets must have been negligibly small. However, patients have to have some variety in their diet, and so the unknown water content of their solid food probably varied to a relatively greater extent.

However, in one rabbit experiment (Figure VIc) the correlation between the two curves was not so good as in the others. Although the two curves did move approximately in parallel, the errors in the crude balance measurements were great enough to obscure the difference in amplitude between the basal and recovery fluctuations.

The few disturbances recorded so far in patients were not the result of a single measurable interference. Almost certainly in the first two (J.C. and T.B.) both water and electrolytes were involved, whereas in the third (G.P.) the true nature of the disturbance must remain a matter for conjecture, although dehydration during the initial fever seems to be a likely factor.

Even in the rabbits it is quite possible that the metabolism of other body constituents, especially electrolytes, may also have been affected by the various interferences; but because of the limitations of the method used, only the overall picture for water could be established. Inspection of the two types of balance curve makes it obvious that whatever else may have been fluctuating, water was certainly concerned to a very large extent.

One should not apply uncritically to humans conclusions drawn from another animal species or *vice versa*. But when an apparently unknown phenomenon, first appearing as a clinical observation, can be deliberately sought and found in an experimental animal, there is a strong suggestion of some underlying mechanism of general physiological importance.

The foregoing data, presenting as they do only an overall pattern of response, can offer very little information as to the intimate details of this mechanism. They do, however, give added support to the hypothesis (Lowe and Sayers, 1952; Lowe, 1953) that the physical concepts of an "open system" are applicable to the control of body water volume. For instance, in both the weight and weight-derived balance curves, the amplitude of the first recovery swing very often exceeded that of the abnormal displacement. This phenomenon of "overswing" may at times be shown by "open" systems, but can never occur in a "closed" system of forces approaching an equilibrium (Burton, 1939).

Furthermore, in the results of the overhydration experiments there is a suggestion that the body is sensitive not only to an osmotic stimulus, but also to a change in its total water volume, or to some fraction of this volume. Thus the recoveries after isotonic sodium chloride infusion (Figure VIB and C) were no more delayed than after a comparable load of isotonic glucose solution (Figure VIA), although the sugar from such an infusion is rapidly metabolized so that the resultant stimulus is very soon the osmotic effect of water alone.

It is now worth while considering the relation of all these recorded findings to the long-term fluctuations of body water content found in œdematous patients by Lowe (1951). For a time these could be regarded only as an abnormality of body volume regulation; but I would now venture to suggest that in those patients the volume-controlling mechanisms may have been normal, yet acting against extreme water loads. This notion would bring all the observations into line with the important general principle in biology that it is only the stimulus which is abnormal, never the response.

SUMMARY

The purpose of this paper is to draw attention to a hitherto unexpected slow phase in the equilibration of body water content. By deliberately ignoring the short-term aspects of this regulation and studying only day-to-day water balances, an overall pattern of long-term recovery has slowly been built up.

After various brief disturbances of water balance there can be large fluctuations of body water content which subside only after several days to the range of fluctuations characteristic of normal. This phenomenon has been observed as a casual occurrence at the clinical level, but a more rigorous demonstration has been possible by an elective study in rabbits. These experimental findings are closely analogous to certain clinical observations in both œdematous and non-œdematous patients, and their theoretical implications for the physiology of water in general are discussed.

ACKNOWLEDGEMENTS

It is a pleasure to thank Dr. T. E. Lowe, Director of the Baker Medical Research Institute and Alfred Hospital Clinical Research Unit, for his continuing inspiration and encouragement of this project, and all those members of the staff who were concerned in the collection and assessment of the human data.

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THE TREATMENT OF TUBERCULOUS MENINGITIS

WITH PARTICULAR REFERENCE TO THE INTRATHECAL TUBERCULIN REACTION[1]

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INFECTION of the meninges by the tubercle bacillus produced a uniformly fatal disease process prior to 1946, when streptomycin was shown to be an effective antibiotic agent in the treatment of tuberculosis. The first recovery from tuberculous meningitis in the Royal Prince Alfred Hospital occurred in 1949, when the patient, an adult male, was treated with intramuscular injections of dihydrostreptomycin, two grammes daily, and the intrathecal administration of streptomycin, 100 milligrammes daily for four months.

During the intervening five years many reports have appeared in the literature of large series of patients treated in various ways with anti-tuberculous drugs, with a tendency to rising recovery rates. However, recovery is often associated with permanent changes in the nervous system, either as a result of the disease process alone or in combination with toxic changes induced by the therapeutic agent.

The outcome in any particular case depends primarily on the stage at which therapy is instituted rather than on the particular pathological process or on the therapeutic regime that is used.

There are many aspects of this problem still requiring closer study, and this paper presents the results of treatment in two cases and the observations made on the changes in the cerebro-spinal fluid during the course of therapy.

REPORTS OF CASES

CASE I.—T.W., a single woman, aged forty-two years, was admitted to hospital in February, 1954. She had been treated for pulmonary tuberculosis in 1950 and for a tuberculous ischio-rectal abscess in 1953. Apart from migrainous headaches, from which she had suffered for many years, she had been well until two weeks before her admission to hospital. At that time she had developed a headache which had steadily increased in severity. She had, in addition, had some giddiness and blurring of vision for several days.

On her admission to hospital she was quite rational, and complained bitterly of her headache. She had a temperature of 101° F., and the only abnormal physical sign was exaggeration of the deep tendon reflexes on the left side of her body. She had no signs of meningism. A full blood count gave results within normal limits; the sputum contained acid-fast bacilli. A skiagram of her chest showed an area of infiltration at the base of the left lung. Lumbar puncture revealed clear cerebro-spinal fluid under a pressure of 200 millimetres, with normal manometric response. It contained 350 white cells, of which 43% were polymorphonuclear cells. Biochemical examination of the fluid gave the following results: the chloride content was 700 milligrammes per 100 millilitres; the sugar content was 64 milligrammes per 100 millilitres; the protein content was 145 milligrammes per 100 millilitres. No organisms were seen on examination of a smear or grown on culture.

A tentative diagnosis of tuberculous meningitis was made, and treatment was commenced with two grammes of streptomycin given intramuscularly and 300 milligrammes of isoniazid given orally per day. No intrathecal therapy was given.

During the next few days her condition appeared to become worse. Her temperature rose above 102° F., the headache became more severe, she began to vomit, and neck stiffness and Kernig's sign made their appearance. The pressure and cell content of the cerebro-spinal fluid climbed rapidly and the percentage of polymorphonuclear cells increased until, five days after the commencement of treatment, the cerebro-spinal fluid was under a pressure of 280 millimetres and contained 1048 cells per cubic millimetre, 98% of them being polymorphonuclear cells.

Treatment with streptomycin and isoniazid was continued, and over the next ten days a remarkable improvement occurred. The temperature fell to 99° F., the headache decreased and appetite returned, signs of meningism completely disappeared and the cerebro-spinal fluid findings returned sharply towards normal. The biochemical findings had remained almost unaltered. These changes are summarized in Figure I.

From this point, her course was one of uninterrupted improvement, with complete loss of symptoms, disappearance of fever and return of cerebro-spinal fluid findings to normal. In six weeks from the commencement of treatment the only abnormal cerebro-spinal fluid findings were the presence of 12 lymphocytes per cubic millimetre (falling to six and three at two months and four months respectively) and a protein content of 40 milligrammes per 100 millilitres. A guinea-pig inoculated with the first specimen of cerebro-spinal fluid developed generalized tuberculosis, but all animals inoculated with later specimens failed to develop the disease.

The dosage of streptomycin was reduced to one gramme daily on the sixteenth day, to 0·5 gramme

[1] Received on January 1, 1955.

daily on the forty-fifth day, and to one gramme bi-weekly on the sixtieth day of treatment. Isoniazid therapy has been continued throughout in a daily dosage of 300 milligrammes.

The pulmonary lesion, which was not extensive, has done well under this antibiotic régime. The patient is now convalescing at a sanatorium and is in good health.

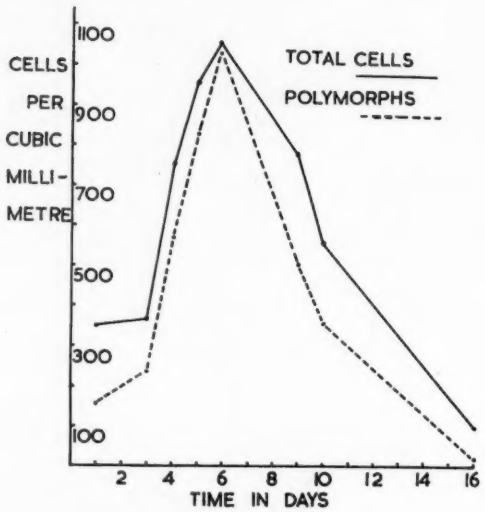

FIGURE I

Cellular changes in the cerebro-spinal fluid in Case I (patient T.W.) during the first sixteen days of treatment to illustrate the intrathecal tuberculin reaction

CASE II.—P.S., a married woman, aged thirty-six years, was admitted to hospital in July, 1954. She had been treated for pulmonary tuberculosis in 1950, and the disease had remained stable under observation at another clinic. Early in June, 1954, she developed a headache which became progressively worse, and by the end of that month she began to vomit. She was then admitted to hospital, when she complained of blurred and double vision and drowsiness of several days' duration.

On her admission to hospital she was obviously ill. She was drowsy and confused and vomited at intervals. Her temperature was 102° F., she had a stiff neck, and Kernig's sign was elicited. The blood count was within normal limits, and her sputum contained no acid-fast bacilli. A skiagram of the chest showed inactive pulmonary tuberculosis. The cerebro-spinal fluid was under a pressure of 165 millimetres, and the responses to the Queckenstedt test were normal. The fluid contained 463 cells per cubic millimetre, 96% of which were lymphocytes. Biochemical examination showed the protein content of the fluid to be 180 milligrammes per 100 millilitres, the sugar content 25 milligrammes per 100 millilitres and the chloride content 640 milligrammes per 100 millilitres. No organisms were seen on examination of a smear or grown on culture.

The same treatment was instituted as in the first case—namely, the intramuscular administration of two grammes of streptomycin per day and the oral administration of 300 milligrammes of isoniazid per day. The result was not so definite as it had been in the first case. The patient's temperature settled slowly and reached 99° F. daily by the nineteenth day. Her mental state also improved, but headache and vomiting persisted. Instead of one high " polymorph peak " of cells in the cerebro-spinal fluid there were three smaller peaks in the first sixteen days (see

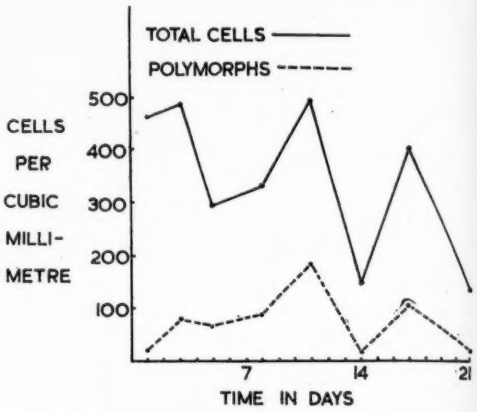

FIGURE II

Cellular changes in the cerebro-spinal fluid in Case II (patient P.S.) during the first twenty-one days of treatment, to illustrate another form of the intrathecal tuberculin reaction

Figure II). The protein content rose steadily and reached 300 milligrammes per 100 millilitres by the sixteenth day.

This rising protein content of the cerebro-spinal fluid together with the persistence of headache and

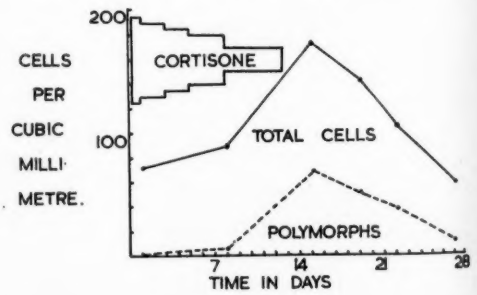

FIGURE III

Cellular changes in the cerebro-spinal fluid in Case II as cortisone dosage was reduced and finally suspended. The final dosage reached represents 25 milligrammes per day. A miniature intrathecal tuberculin reaction may be seen

vomiting and changes in the *fundi oculorum* (engorgement of veins and loss of physiological cup) suggested an incipient subarachnoid block. Intrathecal therapy with 100 milligrammes of streptomycin daily was given a trial, but by the end of three days there had been a rise in temperature and an increase of headache and vomiting, the knee and ankle jerks had disappeared

and the patient had nystagmus on lateral gaze. The intrathecal therapy was promptly suspended and the administration of ACTH was commenced in a dosage of 20 international units every six hours. Headache and vomiting disappeared promptly, the temperature returned to normal and the abnormal nervous signs disappeared within three days. ACTH was continued for two weeks and then replaced by cortisone; the initial dosage was 100 milligrammes daily, and this was gradually decreased over a period of twenty-five days. During this time the patient's clinical condition continued to improve, and examination of the cerebro-spinal fluid showed a gradual fall of cells to 90 per cubic millimetre and of protein content to 180 milligrammes per 100 millilitres. The guinea-pig inoculated with the first specimen of cerebro-spinal fluid developed the disease and thus provided proof of the diagnosis.

After the cessation of cortisone therapy the patient did not feel quite so well for a week. Her temperature rose as high as 100·2° F., and examination of the cerebro-spinal fluid showed a further cell reaction with a "peaking" of the polymorphonuclear cells (see Figure III). Both febrile and cytological reactions quickly subsided, and progress since that time has been uneventful.

Twenty-four weeks after commencing treatment the patient was well. Examination of the cerebro-spinal fluid revealed five lymphocytes per cubic millimetre, and a protein content of 75 milligrammes per 100 millilitres. She continued to receive 300 milligrammes of isoniazid per day, and the streptomycin dosage was reduced to one gramme daily six weeks after the commencement of therapy.

DISCUSSION

Form of Therapy

Lorber (1954*b*) speaks of four stages in the specific treatment of tuberculous meningitis. The first followed the introduction of streptomycin, when the most effective method of administration was being evolved. In the second stage, the intramuscular and intrathecal administration of streptomycin was used as a routine, with the addition of para-amino-salicylic acid. The third stage saw the introduction by Vollum and Smith of tuberculin given by the intrathecal route, whilst the advent of isoniazid ushered in the fourth stage. This still remains a period of uncertainty, particularly concerning the role of intrathecal therapy, now that isoniazid is available. Leading authorities have differing opinions on this aspect of treatment.

Lorber (1954*c*) claims that his carefully compiled results, obtained with a combination of streptomycin given intrathecally and intramuscularly *plus* para-amino-salicylic acid, have yet to be excelled, and feels that the addition of isoniazid serves only to reduce the necessary number of intrathecal injections of streptomycin.

Des Autels and Pfuetze (1954) have not given streptomycin intrathecally since 1949, and the same point of view is put forward by Douglass (1953). The first two authors obtained a survival rate of 60% using streptomycin given intramuscularly *plus* para-amino-salicylic acid, and after isoniazid was added, 14 out of their 16 patients recovered.

Pellegrino, Petrik and Horton (1954) report six cases in children, all of whom did well on streptomycin given intramuscularly and isoniazid. Kerr adds three patients, two of whom were doing badly on streptomycin given intrathecally; all made remarkable recoveries on streptomycin given intramuscularly, para-amino-salicylic acid and isoniazid.

A summary of results from the various forms of treatment may be seen in Table I.

TABLE I

Comparison of Various Forms of Treatment of Tuberculous Meningitis

Authors	Treatment[1]	Cases	Survivors
Lorber (1954*a*)	S *plus* intrathecal	549	253 (46%)
Des Autels and Pfuetze (1953)		22	3
Rubie and Mohun (1949) ..	S	54	18
Gierson and Chamberlain (1953)	SP	16	8
Lorber (1954*b*)	*plus* intrathecal S	38	28
Clark *et alii* (1952)	H	6	4
Gierson and Chamberlain (1953)	SPH	13	11
Pellegrino *et alii* (1954)	SH	6	6
Des Autels and Pfuetze (1954)	SPH	16	14
Kerr (1953) ..	SPH	3	3
Rennie and Read (1955) ..	SH	3	3
Total for SH and no intrathecal therapy	—	41	37

[1] S, streptomycin, given intramuscularly unless otherwise stated; P, para-amino-salicylic acid; H, isoniazid.

It remains a fact that while many lives were saved by streptomycin given intrathecally, a considerable number of patients were left with permanent deafness and moderately severe to severe neurological sequelæ (amounting in all to 36% of the survivors in a series of 549 patients reported by Lorber, 1954*a*). These neurological sequelæ were proportionately related in incidence to the stage at which treatment was commenced, and were attributable to the effects of organized exudate irreversibly involving various parts of the central nervous system. Subarachnoid block was a complication greatly increasing the mortality and morbidity and involving complex neurosurgical procedures for its management. The possible alternative was still more intrathecal medication with tuberculin or streptokinase, which were themselves not free from the risk of untoward reactions.

Boyd (1947) regards the miliary tubercle as the specific reaction of the meninges to the organism, and the formation of exudates as part of a non-specific reaction.

Winifred Bulkeley (1953) reported on the use of ACTH in an attempt to prevent the formation of the exudate and the development of local endarteritis. Her results were encouraging. Even those patients who succumbed and came to autopsy had far less basal exudate than usual, and some had " clean brains ".

We consider that the accumulated evidence favours the abandonment of intrathecal therapy, and now use the following therapeutic regime for adults: (i) streptomycin, given by intramuscular injection in a dose of two grammes per day until a definite response is established, followed by one gramme per day for six months and one gramme twice a week for at least another six months; (ii) isoniazid, 300 milligrammes given orally per day for at least twelve months; (iii) ACTH or cortisone, if any evidence of subarachnoid block appears.

The first patient, who was in a very early phase, made an uncomplicated and uninterrupted recovery. The second patient had a rather longer history when she came under treatment, and though her cerebro-spinal fluid findings improved slowly, she was clinically still ill, and had evidence of increased intracranial tension and commencing subarachnoid block after six weeks of treatment. In view of these findings, it was suggested by a neurological consultant that the intrathecal administration of streptomycin be given a trial. However, as has been noted in the case report, she became so much worse under this form of treatment that it was hurriedly abandoned. ACTH and cortisone completely reversed the ill effects, and her clinical condition improved rapidly. Since that time her progress has been one of steady improvement, and after twenty-four weeks of treatment the only abnormal cerebro-spinal fluid finding is an elevated but falling protein content.

Another patient in the hospital, under the care of Dr. A. W. Morrow, was admitted in a maniacal state with signs of gross meningism and a right-sided abducent nerve palsy due to tuberculous meningitis. Over a period of four months, she too made a good recovery on streptomycin (given by the intramuscular route), isoniazid, para-amino-salicylic acid and a short course of ACTH.

In none of these cases have there been any neurological sequelæ, nor has there been any evidence of streptomycin toxicity.

Behaviour of the Cerebro-spinal Fluid

Rubie and Mohun (1949), in reporting on the early use of streptomycin in tuberculous meningitis, stated that the intrathecal, but not the intramuscular, administration of streptomycin caused pleocytosis in the cerebro-spinal fluid. Smith and Vollum (1950) drew attention to the fact that with a regime of intrathecal and intramuscular administration of streptomycin high " spikes " of cells, containing 60% to 90% of polymorphonuclear cells, appeared in the cerebro-spinal fluid between the fourth and fourteenth days, at about the time when the organisms were disappearing from the cerebro-spinal fluid.

At that time, and indeed to the present day, this common finding was considered to be associated with a chemical irritation of the meninges by the intrathecal administration of streptomycin. However, Swithinbank, Smith and Vollum have stated that streptomycin injected into the normal subarachnoid space does not cause any noticeable cellular reaction. On the other hand, by the introduction of tuberculin into the subarachnoid space of Mantoux-positive controls, they have been able to reproduce the spikes of cells, with polymorphonuclear predominance, and a rise in protein content, very similar to that seen in tuberculous meningitis treated by the intrathecal administration of streptomycin. When they injected 3·75 microgrammes of tuberculin P.P.D. into the thecal space of a Mantoux-positive and otherwise normal person, there occurred a reaction which they describe as the " complete intrathecal tuberculin reaction ". After a lag of ten hours, the body temperature rose to 101·4° F., and the patient felt ill and developed signs of meningism. During the next forty-eight hours this " clinical component " disappeared. In the cerebro-spinal fluid there was an increase of cells reaching a peak after twenty-four hours, of the order of 2000 to 4000 cells per cubic millimetre, polymorphonuclear cells predominating. The cells fell rapidly in number again, but between the fourth and seventh days there occurred a second smaller peak, with lymphocytes predominating. There was also a considerable rise in cerebro-spinal fluid protein content to between 60 and 900 milligrammes per 100 millilitres. These workers also encountered several " anomalous reactions ", in which the clinical component was absent or in which the cellular reaction was monophasic instead of diphasic. As a result of this work, they regarded the cerebro-spinal fluid pleocytosis in tuberculous meningitis as due to an

endogenous tuberculin reaction set off by the tuberculo-protein of organisms killed by intrathecally administered streptomycin, and not to the irritant effect of streptomycin itself.

We have been unable to find any report of the behaviour of the cerebro-spinal fluid in tuberculous meningitis treated with intramuscular streptomycin and isoniazid, without intrathecal therapy which may cloud the issue. None of the authors referred to in the earlier part of this discussion allude to it.

We regard the response in our two cases as a natural endogenous intrathecal tuberculin reaction.

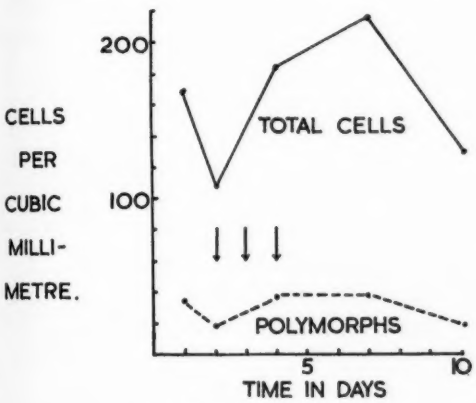

FIGURE IV

Cellular changes in the cerebro-spinal fluid of Case II during intrathecal therapy with streptomycin for three days. One hundred milligrammes were given at each point marked by an arrow. Attention is drawn to the rise in the total number of cells, with a negligible increase in the number of polymorphonuclear cells.

In the first case (see Figure I) there was a single, very high peak of cells with no second phase. It took rather longer than the classical artificial reaction. There was a concurrent clinical component, with an exacerbation of symptoms and the appearance, for the first time, of meningism. The number of cells in the cerebro-spinal fluid rose from 350 to more than 1000 per cubic millimetre, and the polymorphonuclear component reached 98%. These findings, at the time, caused us to make further investigations in an attempt to clarify the diagnosis, which was unproven at the time. However, in retrospect, it is thought that this reaction may prove to be a valuable diagnostic and prognostic feature. The cerebro-spinal fluid protein content in this case was not followed sufficiently closely for us to be able to comment on it.

In the second case (Figure II) there was a series of smaller peaks. The picture was more like that seen when streptomycin was administered intrathecally. The protein content of the cerebro-spinal fluid rose steadily. Again a pronounced symptomatic exacerbation accompanied the cerebro-spinal fluid reaction.

The pronounced, but brief, reaction in the first case, as compared with the longer, less pronounced reaction in the second, may perhaps bear some relation to the stage of the disease; in the first case the disease was in an early stage with its organisms more easily accessible and more rapidly destroyed, and in the second case it was more advanced.

The possibility that eosinophile cells may appear in the cerebro-spinal fluid as part of an antigen-antibody reaction was borne in mind, but none was seen. This is in accord with the findings of Swithinbank, Vollum and Smith in their artificial reaction.

The clinical effects of the intrathecal administration of streptomycin for a few days in our second case have already been mentioned. The course was brief, but we thought, justifiably so. We would draw attention to the fact that its use did cause a low-grade pleocytosis in the cerebro-spinal fluid with a rise of cells from 100 to over 200 per cubic millimetre, in the presence of an atraumatic puncture. However, there was no sign whatever of a reversal of the ratio of polymorphonuclear cells to lymphocytes as in the tuberculin reaction. It is suggested that this perhaps does represent some chemical irritation by streptomycin in the inflamed, as opposed to the normal, subarachnoid space.

ACTH and cortisone, as used in our second case, caused a steady fall of both cells and protein. As cortisone dosage reached low levels, there was a miniature intrathecal tuberculin reaction (Figure III) with fever and malaise, a peak of cells with polymorphonuclear cells predominating, and a long, slow, protein reaction. This suggests that ACTH and cortisone are capable of suppressing the intrathecal tuberculin reaction, which makes its appearance again after the drugs have been stopped. Their value in the prevention of blocks by the suppression of non-specific exudate formation (Boyd) would be in keeping with their action in conditions such as acute rheumatic fever, in which control of the exudative factor is the prime response to the adrenal steroids.

SUMMARY

Most authorities now believe that the intrathecal administration of streptomycin has no place in the treatment of tuberculous meningitis,

and that a regime of streptomycin given intramuscularly and isoniazid, with or without para-amino-salicylic acid, is the treatment of choice.

We have had experience of this treatment in relation to only three adult patients at the Royal Prince Alfred Hospital, but the results, though small, were achieved in one early, one intermediate, and one late case, and are gratifying.

The place of ACTH and cortisone in therapy has been discussed and its value illustrated.

The intrathecal tuberculin reaction of Swithinbank, Vollum and Smith has been described in detail in two cases in which intrathecal therapy was not used. The various forms it may take have been pointed out, and attention is drawn to the apparent suppressive effect of ACTH and cortisone.

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PARAPLEGIA FOLLOWING CHEST SURGERY[1]

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THE complication of paraplegia following operations on the chest is fortunately rare. The following case is reported because an explanation for the complication can be submitted. The explanation may help chest surgeons to avoid a recurrence of such a tragedy. It involves a description of the blood supply of the spinal cord, which is given in some detail because the usual accounts in the various text-books on the subject are either incomplete or inaccurate. The consideration of the anatomy also throws some light on the neurological complications of dissecting aneurysms of the aorta and possibly also of the clinical syndrome of acute transverse myelitis.

CASE HISTORY

The patient, a male, was aged thirty years at the time of his death in 1952. Pulmonary tuberculosis was diagnosed in 1944, when there was bilateral apical infiltration with a cavity at the apex of the right lung. A few months later a right artificial pneumothorax was induced. This was maintained for nearly four years. After it was abandoned the lesion at the apex of the right lung appeared stable, no cavity being visible. In 1949 hæmorrhoidectomy was performed under low spinal anæsthesia. In 1951, after an attack of bronchitis, a large thin-walled cavity was seen in the upper lobe of the left lung. Resection was considered, but for various reasons, including the recurrence of a small cavity at the

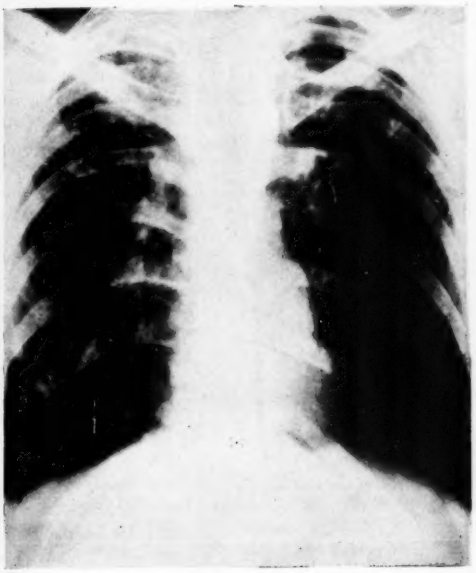

FIGURE I

FIGURE II

Radiograph of the chest on the morning of operation, showing the position of the cavity in the upper lobe of the left lung.

[1] Received on October 23, 1954.

apex of the right lung, was deferred. A course of streptomycin and PAS was given, and although in three months both cavities had decreased in size, resection was still considered premature. In July, 1952, it was thought that dissection of the left cavity would be safer than resection of the upper lobe, and arrangements were made for this to be done (see Figures I and II). Examination of the patient at this time revealed no abnormality other than the pulmonary tuberculosis. The blood pressure was 120 millimetres of mercury, systolic, and 75 millimetres, diastolic.

Operation was performed on August 14, under "Pentothal", curare and nitrous oxide anæsthesia. A standard postero-lateral approach was made, the incision commencing about an inch lateral to the third thoracic spinal process and sweeping laterally and downwards. Most of the fifth left rib except the head was removed. The lung was adherent to the parietal pleura and was freed with difficulty. Over the dorsal lobe posteriorly the dissection was in the extrapleural plane. The cavity was opened and was seen to occupy most of the dorsal lobe and the lower part of the upper lobe with a communication across the fissure. The cavity was dissected with scissors from the underlying lung, the vessels and bronchi being ligated as met with. Bleeding was profuse at all stages necessitating the transfusion of three pints of blood. The incision was closed in layers and two drain tubes were inserted.

Post-operatively the patient's condition was very satisfactory until thirty-six hours later, when he awoke from sleep to find that he could not move his legs. Examination disclosed a complete transverse spinal cord lesion with muscle paralysis and sensory loss below the fifth thoracic segment. Lumbar puncture yielded clear cerebro-spinal fluid under a pressure of 300 millimetres of water. The response to jugular compression was normal and the chemistry and cell count of the fluid were also normal. A tentative diagnosis of ischæmic infarction of the spinal cord was made. X-ray investigation showed no evidence of any bony lesion above the spinal canal. Despite careful and attentive nursing the patient's condition slowly deteriorated, and he died two months after the operation.

Autopsy

Post-mortem examination was performed twenty-four hours later and showed that death had resulted from severe bilateral bronchopneumonia. Cystitis and pyelonephritis were also present. Examination of the spinal canal revealed no bony lesion. After fixation the spinal cord was examined. The dura was opened and appeared normal. The spinal cord showed no abnormality on the surface, except that in the region of the fifth thoracic segment it was moderately depressed and on palpation was appreciably softer than the adjacent cord above and below this level. When sections were examined the softening was seen to be due to virtual liquefaction of the contents of the cord at this level over three to four centimetres of its length.

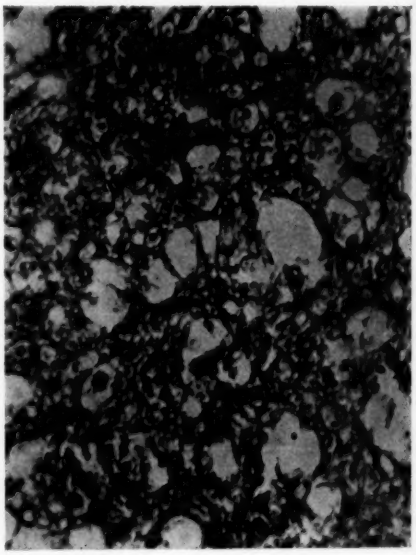

FIGURE III

Histological section of the spinal cord at the fifth thoracic level. Only the glial framework and fat-laden phagocytes can be recognized. (×150)

Microscopic Examination.—The findings on microscopic examination are seen in Figure III. In the first thoracic segment the architecture was easily recognizable, although gross demyelinization was present involving particularly the medial portions of the posterior columns. In the peripheral neurons in the anterior horns degenerative changes were seen.

Demyelinization and vacuolation were more pronounced at the level of the third thoracic segment. There was a circumscribed area of necrosis filled with compound granular corpuscles in one anterior horn. The arterioles had thickened walls and greatly dilated lumina filled with red cells.

In the fourth thoracic segment more pronounced degenerative changes were present, the anterior horns being barely recognizable owing to disruption and necrosis of neurons with infiltration of *Gitter* cells. The whole area of the cord was involved.

In the fifth thoracic segment there was complete disorganization of the cord, only a fragmented web-like structure remaining in which were numerous compound granular corpuscles. Pronounced necrosis was still visible between the fifth and sixth thoracic segments, but the section was obviously below the main level of the lesion.

DISCUSSION

When a normal spinal cord is examined in transverse section, it can be seen that its blood supply is derived from a large anterior spinal artery about the ventromedian sulcus and by posterior spinal arteries, one or two on each side about the dorso-lateral sulci. The anterior spinal artery supplies approximately the anterior two-thirds of the cord, or, according to the investigations of Bolton (1939), as much as the anterior seven-eighths. The anterior and posterior spinal arteries are formed from the anterior and posterior radicular arteries respectively, which reach the spinal cord along the anterior and posterior nerve roots. These radicular arteries arise in their turn from the division of a segmental intervertebral artery in the intervertebral foramen. At the upper end of the spinal cord contributions to both systems are received from the vertebral arteries. There is anastomosis between the two systems both within and around the cord, but this anastomosis is not extensive.

The cervical and upper thoracic regions of the cord derive their intervertebral arteries from the deep cervical arteries and the superior intercostal arteries. The aorta gives rise to the intercostal and lumbar arteries, which supply the last ten thoracic segments and the lumbosacral segments of the cord (Figure IV). The lowermost two lumbar arteries do not supply the cord itself, but with the iliolumbar and the lateral sacral arteries supply the roots of the *cauda equina*.

The painstaking researches of Kadyi (1889) and of Suh and Alexander (1939) have demonstrated that many radicular arteries are insignificant and are expended entirely in furnishing the blood supply to the nerve root, making no significant contribution to the spinal cord. There are only six to eight large radicular arteries accompanying the anterior roots and from five to eight posterior radicular arteries, and usually large anterior and posterior radicular arteries do not occur at the same level. The distribution of these large anterior radicular branches is irregular and asymmetrical. Common sites are the fourth or fifth cervical segments, the first thoracic and one of the lower thoracic segments and the second lumbar segment. Frequently none are seen in the middle thoracic region but if one is present it is found most frequently accompanying the fifth, sixth or seventh anterior root. When the

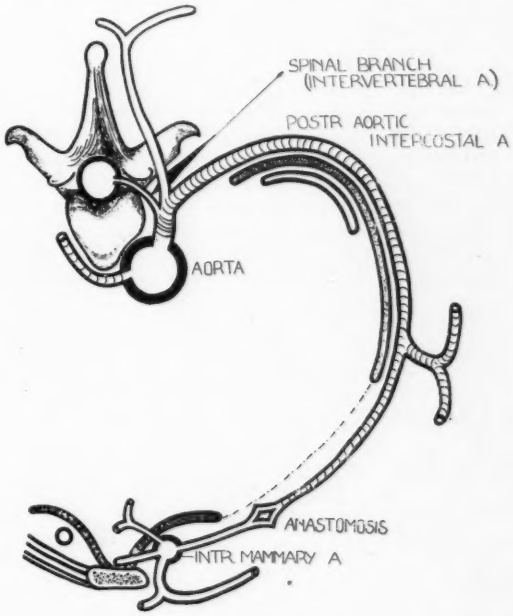

FIGURE IV

A diagram to show the origin of the spinal (intervertebral) artery. (Modified from Grant, 1944)

radicular artery reaches the spinal cord it forms the anterior spinal artery by dividing into an ascending and a descending branch, through which it establishes anastomosis with a large anterior radicular branch above and below. This explains the great variations in character of the anterior spinal artery at different levels of the cord. The usual conception of the anterior spinal artery is of a long channel running the entire length of the spinal cord. Although a continuous arterial channel exists, it is essentially a chain of anastomoses.

With regard to the posterior spinal arteries, no continuous channel is formed at all.

Myelomalacia may follow obstruction of a large radicular branch. Occasionally large anterior and posterior radicular branches enter on the same side of the cord at the same level, the two arteries being derived from the bifurcation of the intervertebral vessel entering through the intervertebral foramen. It is submitted that this arrangement held for our patient, and that either the intervertebral branch of the intercostal artery or the intercostal artery itself proximal to the origin of the intervertebral branch was ligated during the operation or became thrombosed soon afterwards.

The relative rarity of occurrence of a major spinal branch in the middle thoracic region would help to account for the fact that this complication is so uncommon.

Reflection on this case report supports the suggestion of Schwartz, Shorey and Anderson (1950) that some otherwise unexplained cases of transverse myelitis may be the result of thrombosis of a major radicular artery. These authors have advanced reasons for the occurrence of myelomalacia as the result of dissecting aneurysm of the aorta which depends upon the details of the spinal vascular system outlined above. According to the arc of the aortic wall involved and the length of the dissection, several intercostal arteries may be obstructed or actually torn away near their origin.

SUMMARY

A description is given of the case in which ischæmic necrosis of the spinal cord followed a chest operation.

A brief review of the anatomy of the spinal cord blood supply is given.

Attention is drawn to the danger of damaging the intercostal artery proximal to the spinal branch (intervertebral artery).

ACKNOWLEDGEMENTS

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THE COMPARATIVE EFFECTS OF RADIATION AND OF LEAD ON CERTAIN ASPECTS OF THE STRUCTURE OF LYMPHOID CELLS[1]

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In a previous paper (Shiels, 1954) I have shown that, for a group of persons exposed at their work to irradiation associated with X-ray work or the use of radioactive substances, (*a*) the mean ratio of monocytes *plus* large lymphocytes to small lymphocytes was significantly greater, and (*b*) the mean percentage of lymphocytes which showed granules in the cytoplasm when stained by Leishman's stain was significantly less, than the respective mean values for persons not exposed to irradiation.

In a further investigation not yet published I have shown that for each member of a group of six persons who were examined before exposure to irradiation and again after several months' exposure at their work, there were found an increase in the ratio at the second examination, the mean increase being statistically significant, and a decrease in the percentage of lymphocytes showing granules in the cytoplasm, the mean decrease being statistically significant. Further, for each member of this group there was at the second examination an increase in the percentage of monocytes which were of the particular type previously described (Shiels, 1954), the mean increase being statistically significant.

Present Investigation

The present paper contrasts the effect of irradiation and of lead on these three aspects of the structure of the lymphoid cells. Monocytes have been included in the category "lymphoid type".

The three factors mentioned above were determined by the technique already described, in films stained by Leishman's stain, for a group (Group A) of from 36 to 41 persons (according to the type of test) who were exposed at their work to irradiation from X-ray machines or radioactive substances, for a group (Group B) of 34 persons not exposed to irradiation or to lead, and for a group (Group C) of 30 persons who were suffering from lead poisoning at the time of the tests, but had not been exposed to irradiation.

The cases of lead poisoning were diagnosed by the Industrial Hygiene Division, Department of Health, Victoria, by the clinical signs and/or symptoms in conjunction with the following laboratory findings: the stippled cell count, the urinary lead concentration (milligrammes per litre and microgrammes per gramme of solids in the urine), the concentration of coproporphyrin in the urine, and in some cases the concentration of lead in the blood.

Records are not available as to the intensity of exposure to irradiation for all the subjects; but for those subjects for whom estimates by means of monitoring films were available, the exposure was well below the accepted tolerance dose of 0·3*r* per week (free air dose).

It is considered that such conditions would also have applied with the other subjects.

Results

Comparison of the Ratios in the Three Groups

It has been shown (Ferguson and Ferguson, 1934; Shiels, 1936, 1937, 1950) that the ratio of monocytes *plus* large lymphocytes to small lymphocytes is increased by absorption of lead, the ratio falling again when lead poisoning is present or imminent. Shiels (1954) has shown that this ratio is greater for a class of persons exposed to irradiation than for a class of normal persons. It was of interest, therefore, to determine whether there was a significant difference in the values of the ratios for persons exposed to irradiation and for persons who were suffering from lead poisoning. The results of this investigation are shown in Table I.

Statistical analysis of the results by the Aspin Welch test indicates that the means for the two classes of persons (Groups A and C) are significantly different at the $P<0{\cdot}01$ level.

[1] Received on November 2, 1954.

TABLE I

The Ratios of Monocytes plus Large Lymphocytes to Small Lymphocytes for the Three Groups of Persons

Range of Values	Group A: Exposed to Irradiation		Group B: Not Exposed to Irradiation or to Lead		Group C: Suffering from Lead Poisoning	
	Number in the Range	Percentage of Total in Group	Number in the Range	Percentage of Total in Group	Number in the Range	Percentage of Total in Group
0·0 to 0·5	0	0	0	0	0	0
0·6 to 1·0	0	0	0	0	1	3·3
1·1 to 1·5	0	0	6	16·7	4	13·3
1·6 to 2·0	3	7·3	11	30·6	14	46·7
2·1 to 2·5	10	24·4	12	33·3	7	23·3
2·6 to 3·0	4	9·8	0	0·0	3	10·0
3·1 to 3·5	6	14·6	3	8·3	0	0
3·6 to 4·0	5	12·2	0	0·0	0	0
4·1 to 4·5	1	2·4	1	2·8	0	3·3
4·6 to 5·0	2	4·9	2	5·6	0	0
5·1 and over	10	24·4	1	2·7	0	0
Total	41	100·0	36	100·0	30	99·9
Mean	3·8		2·4		2·04	

It has been shown in various papers (Shiels, 1936, 1937, 1950) that the mean ratio for persons with plumbism is about the same as that for normal persons.

Comparison of the Percentage of Lymphocytes Showing Granules in the Cytoplasm for the Three Groups

Previous work (Shiels, 1954) has shown that the percentage of lymphocytes showing granules in the cytoplasm in stained films is greater for the large than for the small lymphocytes. Since the effect of exposure to irradiation is to increase the ratio of large to small lymphocytes (unpublished work), and the effect of lead poisoning is to reduce it, one might expect that the percentage of lymphocytes showing granules in the cytoplasm for persons exposed to irradiation would be greater than, and for those suffering from lead poisoning less than, the

TABLE II

The Percentage of Lymphocytes with Granules in the Cytoplasm

Range of Percentages of Lymphocytes with Granules in Cytoplasm	Group A: Exposed to Irradiation		Group B: Normals		Group C: Suffering from Lead Poisoning	
	Number in the Group.	Percentage of Total in the Group	Number in the Group	Percentage of Total in the Group	Number in the Group	Percentage of Total in the Group
0 to 5	6	17·7	0	0	0	0
6 to 10	2	5·9	0	0	0	0
11 to 15	4	11·8	0	0	0	0
16 to 20	7	20·6	0	0	0	0
21 to 25	4	11·8	1	2·8	0	0
26 to 30	2	5·9	5	13·9	0	0
31 to 35	4	11·8	6	16·7	2	6·7
36 to 40	2	5·9	5	13·9	0	0·0
41 to 45	2	5·9	3	8·3	2	6·7
46 to 50	1	2·9	7	19·4	3	10·0
51 to 55	0	0	3	8·3	1	3·3
56 to 60	0	0	4	11·1	5	16·7
61 to 65	0	0	0	0·0	4	13·3
66 to 70	0	0	2	5·5	3	10·0
71 to 75	0	0	0	0·0	5	16·7
76 to 80	0	0	0	0·0	1	3·3
80 and over	0	0	0	0·0	4	13·3
Total	34	100·22	36	99·9	30	100·0
Mean percentage	20·62	—	—	42·36	—	62·45
>51%	—	0	—	24·9	—	76·6
>61%	—	0	—	5·5	—	56·6

respective values for a class of normal persons. Such is not the case. The results are shown in Table II.

The mean percentage of lymphocytes showing granules in the cytoplasm for the group of normal subjects (Group B) was 42·36, which is in the range 41% to 45%. Of the 27 values above this range in Groups A and C, 26 or 96·3% were in Group C, and of the 33 values below this range 31 or 93·9% were in Group A.

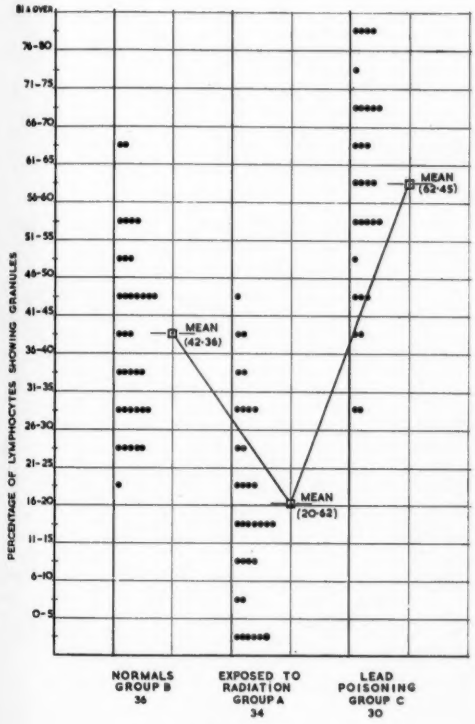

FIGURE I

Range of percentages of lymphocytes showing granules in the cytoplasm

Inspection of Table II shows that, compared with the mean percentage of lymphocytes which show granules in the cytoplasm for a group of normal persons, there is a significantly higher mean percentage for a group of persons suffering from lead poisoning, the mean being about one and a half times as great ; for the group of persons exposed to irradiation the mean percentage is only half what it is for the group of normal subjects. For the group of persons suffering from lead poisoning the mean is three times the mean for the group of persons exposed to irradiation. A statistical analysis of these results is shown in Table III.

TABLE III

Statistical Analysis of the Findings in Table II

Groups Compared	t[1]	n[1]	P[1]	Significance of t
Group A (34) } Group B (36) }	7·541	68	0·001	Highly significant
Group B (36) } Group C (30) }	6·134	64	0·001	Highly significant
Group A (34) } Group C (30) }	11·66	62	0·001	Highly significant

[1] The t values (Fisher, 1950) were determined by comparison of the means, and the corresponding P values from Fisher and Yates's tables (1949).

Comparison of the Percentages of Monocytes which are of a Particular Type in Groups A and C

The particular type of monocyte (designated " B " type) has already been described (Shiels, 1954). A somewhat similar type of monocyte has been described by Browning (1949) in the blood of persons exposed to irradiation from radioactive paints. However, the " abnormal " monocytes she described were absent from normal blood (which was not the case for the monocytes of " B " type), and had disappeared

TABLE IV

The Incidence of Monocytes of Type " B " in Subjects Exposed to Irradiation (Group A) and in Persons Suffering from Lead Poisoning (Group C)

Range of Percentages of Monocytes of the Particular Type	Group A		Group C	
	Number in the Range	Percentage of the Group in the Range	Number in the Range	Percentage of the Group in the Range
0 to 5	0	—	1	4·8
6 to 10	0	—	0	0·0
11 to 15	0	—	1	4·8
16 to 20	1	2·7	0	0·0
21 to 25	1	2·7	2	9·5
26 to 30	2	5·4	4	19·0
31 to 35	4	10·8	4	19·0
36 to 40	5	13·5	3	14·3
41 to 45	4	10·8	3	14·3
46 to 50	4	10·8	1	4·8
51 to 55	3	8·1	2	9·5
56 to 60	5	13·5	0	0·0
61 to 65	4	10·8	0	0·0
66 to 70	3	8·1	0	0·0
71 and over ..	1	2·7	0	0·0
Total	37	99·9	21	100·0
Mean percentage of monocytes of the particular type	47·27	—	33·67	—

from the blood of the luminizers after they had been away from the hazard for some months. The percentages of the monocytes which were of this type (" B ") were determined in the blood films of 37 persons in Group A and of 21 persons in Group C. Table IV shows the range of percentages in the two groups.

The t value for the comparison of the means was 3·756, which for an n value of 56 corresponds to a P value of less than 0·001. There is, therefore, a highly significant difference between the two groups for the mean percentages of monocytes which are of the particular type " B ".

COMMENT

At the present time, the explanation of the three effects demonstrated is not known. Various interesting speculations could be put forward, but it is considered advisable to let these await further work.

None of the persons in Group A was exposed to the generally accepted tolerance doses; indeed, in nearly all cases they were exposed to very much less. It may be of some significance, therefore, in regard to the percentage of lymphocytes with granules in the cytoplasm, that doses less than the generally accepted tolerance doses produced an effect in one direction equal in magnitude to the effect in the other direction produced by amounts of lead sufficient to cause clinical lead poisoning.

SUMMARY

In a group of persons suffering from lead poisoning, the mean percentage of lymphocytes which show granules in the cytoplasm is significantly greater than in a group of normal persons, and very much greater still than in a group of persons exposed to less than the accepted tolerance irradiation doses from X-ray sources, and/or radioactive substances.

The mean ratio of monocytes *plus* large lymphocytes to small lymphocytes in a group of persons exposed to irradiation is significantly greater than the mean value in a group of lead poisoned persons.

The mean percentage of monocytes which are of a particular type in a group of persons exposed to irradiation is significantly greater than the mean percentage in a group of lead poisoned persons.

ACKNOWLEDGEMENTS

Acknowledgement is made to Mrs. W. Van den Berg, Technical Assistant in the Industrial Hygiene Laboratories, for her care in the preparation of slides, and to Associate Professor M. H. Belz and Miss A. G. Doig, of the Department of Mathematical Statistics, University of Melbourne, for advice in regard to the statistical analysis.

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SCLERODERMA WITH HEART FAILURE[1]

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SCLERODERMA is a disease of the collagen system, which affects not only the skin, but also internal organs such as the intestinal tract, the lungs, the endocrine glands, the nervous system and the kidneys, as well as skeletal muscles, bones and joints. Many of the patients in the older literature were said to have died from heart failure, but specific cardiac involvement has been described only since the case reports of Matsui (1924), of Brock (1934) and in particular of Weiss *et alii* (1943). It is the purpose of this paper to report a case of scleroderma and heart failure and analyse the ways in which the cardiovascular system may be involved in the sclerodermatous process.

REPORT OF A CASE

Mr. G.W. first noticed stiffness, swelling and pain in the left hand when playing the piano in March, 1946, at the age of forty-three years. Two months later he suffered from a febrile illness of gradual onset with cough, sputum and dyspnœa, for which he was treated with sulphonamides. He responded only very slowly, and convalescence was complicated by gross painless swelling of the right foot and leg due to right femoral venous thrombosis. Shortly afterwards, in July, 1946, he developed œdema of the face, hands and both legs and a swinging pyrexia, and was admitted on August 4 to the Royal Melbourne Hospital. At the time clinical examination revealed no abnormal signs in the heart or abdomen; examination of the chest disclosed a few coarse rales posteriorly at the base of the right lung. There were non-tender swelling of both hands and wrists, swelling of the left ankle and pitting œdema of the right leg up to the knee. X-ray examination of the chest revealed general thickening of the pulmonary trunks, heavy hilar shadows, and diffuse vague mottling through the lungs. The X-ray picture suggested Boeck's sarcoid. An electrocardiogram was normal and renal function tests revealed no abnormality; but serum colloidal gold and cephalin-flocculation tests showed some evidence of parenchymal hepatic damage. A lymph-gland biopsy, taken in view of the X-ray report on the chest, revealed no evidence of sarcoidosis. He was discharged from hospital, much improved, on September 3, without a definitive diagnosis having been established.

From October, 1946, to 1951 he was sufficiently well to carry on his profession as a teacher, but was still handicapped by stiffness and pain in both hands and by increasing dyspnœa, which precluded almost any physical exertion. In August, 1951, he suffered a further severe respiratory infection, which was accompanied by a recurrence of swelling of the right leg. An X-ray film of the chest taken at that time was said to reveal no abnormality. In April, 1952, his general health deteriorated, dyspnœa became much more severe, and he was told that his heart was seriously diseased. An electrocardiogram taken at that time revealed the presence of a right bundle branch block. Towards the end of the year he was forced to stop work, the œdema gradually returned, and from then on regular injections of mercurial diuretics were necessary to keep the swelling under control.

His presenting symptoms, when he was first examined by the writer in April, 1953, could be summarized as follows: (i) dyspnœa on minimal exertion but not at rest, slight but definite orthopnœa; (ii) œdema of both ankles; (iii) cough, with some mucoid sputum; (iv) stiffness of both hands, limitation of movement, inability to make a fist or straighten fingers; (v) periodic pallor and cyanosis of both hands with numbness and tingling whenever they were exposed to cold and quickly relieved by warmth—this last-mentioned symptom having been present for about a year. His appetite was good, his weight was constant and he was not aware of any difficulty in swallowing food. There were no relevant symptoms in any of the other systems.

Physical examination of the patient gave the following information. The skin of his hands was thick and indurated, darkly pigmented, shiny and atrophic and adherent to the subcutaneous tissues. The terminal phalanges were tapering towards the finger tips, and small scars were present over the tips of the second and third fingers of both hands. The skin involvement was of such a degree that only limited finger movement was possible; but although ulnar deviation was present at both wrists there was no actual joint deformity to complicate the appearance. The skin of the toes and face was similarly involved with areas of pigmentation and depigmentation. The skin over the nose and cheeks was shiny and atrophic, with numerous red telangiectatic areas. There was a lack of facial lines and paucity of facial movements reminiscent of the Parkinsonian facies. Hard subcutaneous nodules were palpable in the region of both elbow joints over the olecranon processes, not fixed to the underlying bone structure. Immersion of both hands in cold water produced typical Raynaud's phenomenon with blanching associated with subjective tingling and pain, rapidly relieved by warmth.

The pulse was small with regular sinus rhythm (92 per minute), the blood pressure was 120 millimetres of mercury, systolic, and 80 millimetres, diastolic. The jugular venous pressure was greatly raised with a large collapsing systolic wave suggesting tricuspid incompetence. The lung bases were clear, but the liver was enlarged to three fingers' breadth below the right costal margin and pulsated. There was bilateral pitting œdema of the lower extremities. The apex beat was displaced to the left, the cardiac impulse being maximal in the sixth left intercostal space, 10 centimetres from the mid-line. A triple heart rhythm was clearly audible at the apex, and the second pulmonary sound was widely split and accentuated. A grade two systolic murmur was

[1] Received on August 25, 1954.

present over the entire precordium, maximal at the apex. Examination of the ocular fundus revealed no abnormality. Examination of the lungs revealed symmetrically poor expansion, movement of the chest wall being generally limited, but no other abnormality. As well as the pulsating liver, the spleen was easily palpable two fingers' breadth below the costal margin. There were no abnormal signs in the central nervous system. The urine contained a faint cloud of albumin.

Laboratory investigations gave the following additional information. The hæmoglobin value was 13·1 grammes *per centum*, the white blood cells numbered 4700 per cubic millimetre, the differential count being normal, the blood sedimentation rate was eight millimetres in one hour, and the blood gave a negative response to the Wassermann test. The blood

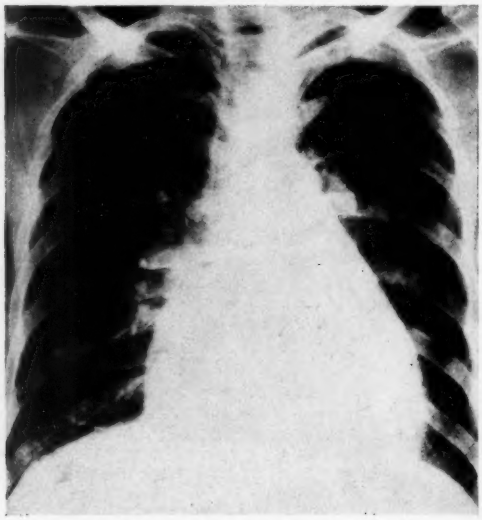

FIGURE I

X-ray film of chest showing cardiac enlargement with triangular heart shadow, and pulmonary congestion with fine reticulation of both lower zones

urea content was 33 milligrammes per 100 millilitres, the blood calcium content 9·6 milligrammes per 100 millilitres, and the blood inorganic phosphorus content 3·5 milligrammes per 100 millilitres. The basal metabolic rate was estimated at −1%. The Kepler test for adrenal function gave a normal response.

X-ray studies gave the following information. In the chest (Figure I) cardiac enlargement was present with a triangular heart shadow, pulmonary congestion with fine reticulation over both lower zones. In the hands (Figure II) there was early bony resorption of the terminal phalanges, best seen in index finger of the right hand. Around both elbow joints (Figure III) there was patchy calcification of soft tissues typical of *calcinosis circumscripta*. X-ray examination after a barium meal revealed no abnormality in the upper part of the intestinal tract.

An electrocardiogram showed right bundle branch block with a tall secondary *R* wave in the right chest leads and a prolonged *P-R* interval (Figure IV). A punch biopsy of the skin taken from the dorsum of the right hand was reported on by the pathologist, Dr. V. J. McGovern, as showing typical scleroderma (Figure V).

In order to study the physiological mechanism underlying the cardiac failure, cardiac catheterization was carried out by the staff of the Hallstrom Institute of Cardiology on May 1, 1953, with the following results: (i) Resting values: cardiac output, 3·8 litres per minute; pulmonary artery pressure, mean,

FIGURE II

Tufting due to bony resorption of the terminal phalanges

FIGURE III

Patchy calcification of soft tissues in vicinity of elbow joint typical of *calcinosis circumscripta*

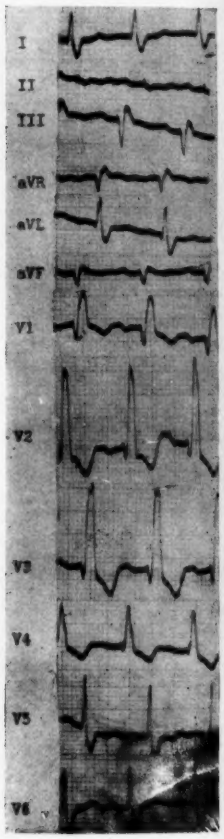

FIGURE IV

Electrocardiogram showing right bundle branch block with tall secondary *R* waves in right ventricular surface leads and prolonged *P-R* interval

30 millimetres of mercury (45/22); right ventricular pressure, mean, 22 millimetres of mercury (50/8); right auricular pressure, mean, 12 millimetres of mercury; brachial artery pressure, mean, 78 millimetres of mercury (101/63); arterial oxygen saturation, 96%. (ii) After one milligramme of lanatoside C given intravenously: cardiac output, 5·1 litres per minute; pulmonary artery pressure, 33 millimetres of mercury (58/26); right ventricular pressure, mean, 23 millimetres of mercury (56/6); right auricular pressure, mean, 15 millimetres of mercury; brachial

artery pressure, mean, 86 millimetres of mercury (120/68); arterial oxygen saturation, 94%.

The tip of the catheter could be advanced to the right border of the cardiac shadow, so that a large pericardial effusion was excluded (Figure VI). The right auricular pressure tracing showed a large "c" wave, confirming the presence of tricuspid incompetence (Figure VII). There was definite evidence of improved cardiac function after a digitalizing dose of the cardiac glucoside lanatoside C.

During the period of these investigations the patient was admitted to the Royal Prince Alfred Hospital, Sydney. He was treated by digitalis, mercurial

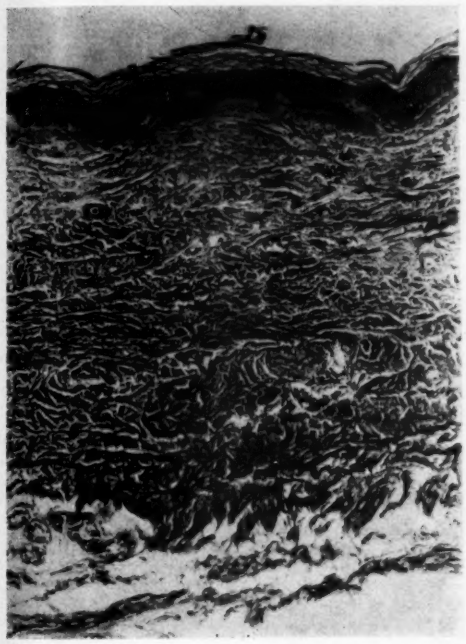

FIGURE V

Biopsy of skin, showing the typical changes of scleroderma with dense collagen replacing the normal *cutis vera* and atrophy of the overlying epithelium (Hæmatoxylin and eosin. ×75)

diuretics and sodium restriction, to which he responded satisfactorily, with diminution of œdema and fall in venous pressure. He was discharged from hospital on June 17, 1953, and the same therapeutic regime was continued at home. Shortly afterwards, on July 15, at the age of fifty years, he suddenly died in his sleep, although the day before he had appeared to be in his usual state of semi-invalidism.

Autopsy Findings

Autopsy was performed thirty hours after death by Professor F. R. Magarey.

The skin was tightly drawn on the face and the backs of hands. There was slightly mottled pigmentation, particularly pronounced on the back of the hands. Pigmentation was present over the lower end of the right tibia. The thyroid gland was normal, as were the œsophagus, larynx and trachea. The main bronchi were congested and the lumen contained mucopus, especially on the left. The right lung weighed 1000 grammes, the left 860 grammes, and both pleural cavities contained a little yellow fluid. The whole of

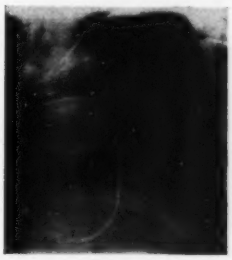

FIGURE VI

Cardiac catheter within the heart

the lower lobe of the right lung and the posterior portion of the upper lobe were red, airless and very firm. In the cut surface a fine honeycomb pattern was present. The rest of the upper lobe and the middle lobe were œdematous. Examination of the left lung

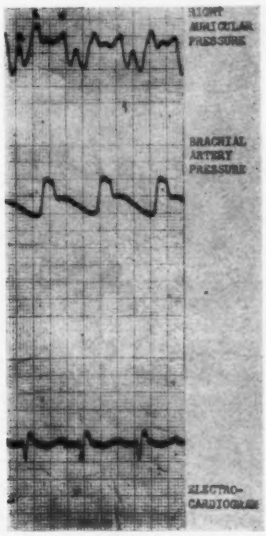

FIGURE VII

Right auricular pressure tracing showing the large "c" wave of tricuspid incompetence, with simultaneous brachial artery pressure tracing and electrocardiogram, lead III

showed that, except for the anterior border and the apex of the upper lobe, which were œdematous, the lung was firm and had the same appearance as did the right. There were old organized adhesions anteriorly and medially over the upper lobe.

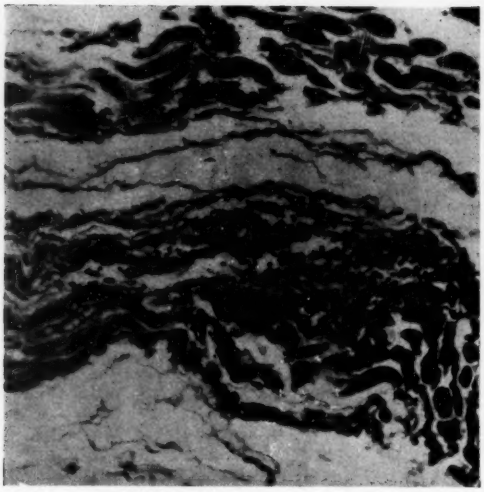

FIGURE VIII

Photomicrograph of psoas muscle, showing a collection of lymphocytes in the centre of which is a small vessel cut tangentially, which shows hyaline degeneration of the wall. (Hæmatoxylin and eosin. ×150)

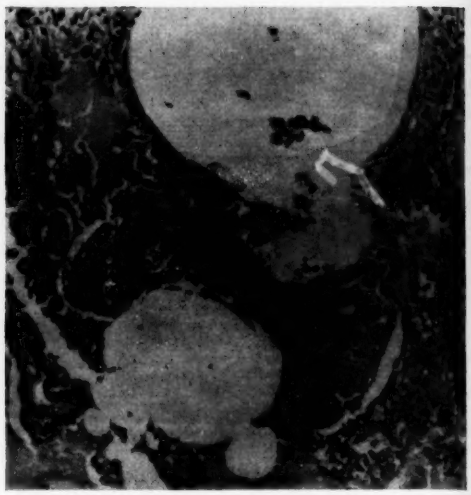

FIGURE X

Photomicrograph of anterior portion of left lung. The alveoli are irregularly dilated and contain œdema fluid together with some pulmonary macrophages. The alveolar walls are thickened and infiltrated with lymphocytes. (Hæmatoxylin and eosin. ×150)

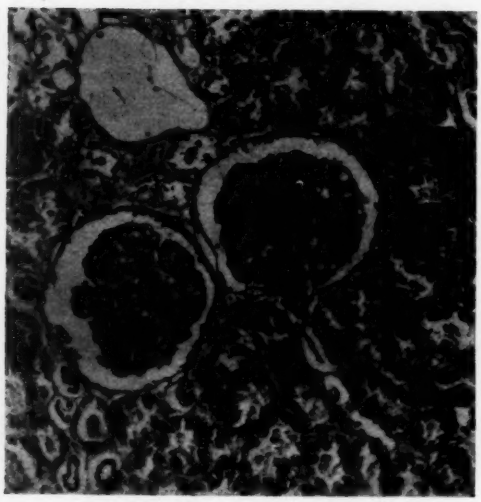

FIGURE IX

Photomicrograph of kidney. The basement membrane of the capillary loops shows fairly diffuse hyaline thickening causing many of the capillaries to remain abnormally patent. (Hæmatoxylin and eosin. ×150)

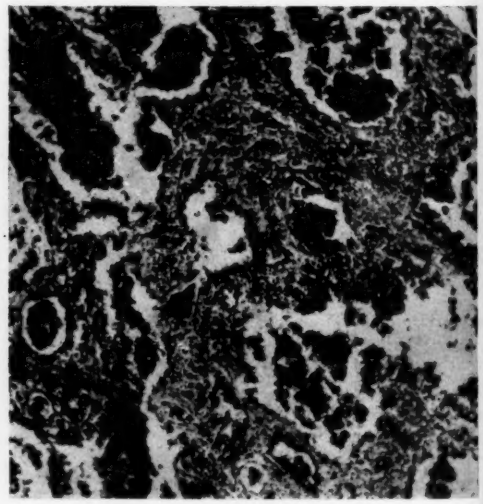

FIGURE XI

Photomicrograph of right lung. There is widespread intraalveolar hæmorrhage. The alveolar walls are fibrotic and much more thickened than in Figure XII. Many lymphocytes are still present. (Hæmatoxylin and eosin. ×75)

The heart weighed 460 grammes. The pericardium contained 30 millilitres of yellow fluid. There was no pericarditis. The right ventricle was dilated and greatly hypertrophied; slight dilatation of the left was evident. The right auricle was moderately dilated, and the tricuspid valve admitted four fingers. The left auricle was normal, and the mitral valve admitted three fingers. The pulmonary artery and its main branches were dilated and slightly atheromatous. The myocardium was normal in appearance and consistency. No abnormality was detected in the endocardium and valves. There were craggy calcified deposits at the origin of both cœliac axes and superior mesenteric artery. The aorta was free of atheroma. Examination of the coronary arteries showed slight atheroma with calcification, but they were widely patent. The right femoral vein from Poupart's ligament to the popliteal space was criss-crossed with old organization of thrombus. In the thorax, the lymph glands at the bifurcation of the trachea and along the aorta were enlarged, light grey and gelatinous looking.

The peritoneal cavity contained 300 millilitres of turbid brownish fluid, in which were gelatinous fibrinous clots. There were areas of spotty pigmentation on the peritoneum in the recto-vesical pouch. The liver weighed 2100 grammes. It had a smooth surface and a normal lobular pattern and was rather firm. The spleen was much enlarged, weighing 510 grammes; it was dark red and firm, and Malphigian corpuscles were visible. Each kidney weighed 205 grammes; slight capsular adhesions were present and the cortex was slightly swollen. The adrenal glands were smaller than normal and the cortex was narrowed. The other abdominal organs were normal. No abnormality was detected in the brain or pituitary.

The voluntary muscles were normal on naked-eye examination. In the region of the right elbow there were chalky calcified deposits, apparently confined to the cutis.

The findings on microscopic examination were as follows. The left ventricle, interventricular septum, small intestine, œsophagus, right and left adrenals, thyroid and pituitary were all normal. In the psoas muscle (Figure VIII) there were sparse collections of lymphocytes in the connective tissue about the larger blood vessels, an occasional one of which showed hyaline degeneration of its media. In the liver were found the changes of chronic venous congestion. Examination of the spleen revealed moderate congestion of the pulp, the sinusoids being dilated by the blood they contained. Examination of a paraaortic lymph node showed that the lymphocytes in the follicles were separated from one another by intercellular fluid and there was sinus catarrh. In the skin of the hand changes typical of scleroderma were present. Dense collagen was present throughout the whole depth of the cutis, and there was atrophy of the overlying epithelium with increased melanin in the basal layer. In the nodules of the elbow region there were areas of amorphous calcification which ran mainly longitudinally in the direction of the laminæ of collagen fibres. There was very little associated cellular reaction. In the right index finger were found resorption of bone of the dorsal aspect of the tip of the terminal phalanx and replacement by rather vascular connective tissue. In the femoral vein there was an organized thrombus of long standing, which had been replaced by dense collagen in which were hæmosiderin granules. Recanalization had occurred. In the kidney (Figure IX) all the glomeruli showed slight generalized hyaline thickening of the basement membrane of the capillary loops of the glomerular tufts. This caused the lumen of many of the capillaries to remain abnormally patent. The lung findings are shown in Figures X, XI and XII. Examination of a section from the anterior border of the upper lobe of the right lung showed that the larger branches of the pulmonary artery contained athero-sclerotic plaques, whilst in many of the smaller arteries well-developed *endarteritis obliterans* was present. The alveolar capillaries were congested. The air spaces were irregularly dilated and contained œdema fluid in which were many pulmonary macrophages. The alveolar walls were somewhat thickened and cellular collections of lymphocytes could be seen in the interstitial tissue. In many alveoli the epithelium had become cuboidal. Examination of a section from the lower lobe of the right lung revealed a much greater degree of engorgement, and there was widespread interalveolar hæmorrhage. The dilatation of the air sacs was more advanced and the alveolar walls were more thickened.

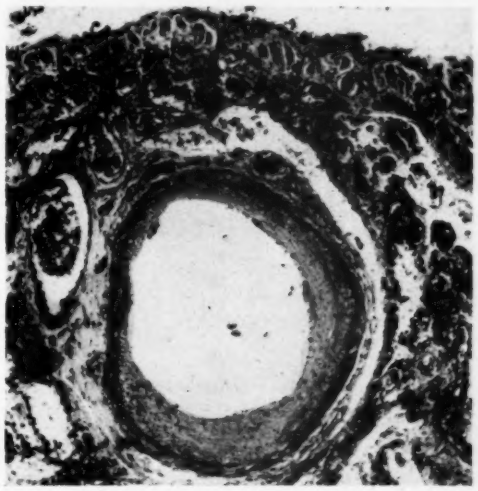

FIGURE XII

Photomicrograph of right lung. The artery shows intimal proliferation, and there is extreme engorgement of the submucous vascular plexus seen at the top of the picture. (Hæmatoxylin and eosin. ×75)

The final pathological diagnosis may therefore be summarized as follows: (i) pulmonary fibrosis due to scleroderma; (ii) pulmonary heart disease with right ventricular hypertrophy and functional tricuspid incompetence; (iii) congestive cardiac failure; (iv) right femoral venous thrombosis; (v) renal lesions of scleroderma; (vi) scleroderma of skin; and (vii) *calcinosis circumscripta*.

DISCUSSION

It has been recognized for many years that scleroderma is a widespread disease of the collagen system affecting at times most of the organs of the body, quite apart from the better known changes in the skin. Reviews of the subject have been published by Matsui (1924), by Goetz (1945), by Beerman (1948), by Truelove and Whyte (1951), by Cullinan (1953) and by Harper (1953). In fact, it has been

stressed by Goetz (1945) and Cullinan (1953) that in view of these disseminated lesions the term scleroderma is a misnomer, and these authors suggest the more embracing title of " diffuse systemic sclerosis ".

Thibierge-Weissenbach Syndrome (Skin Changes, Raynaud's Phenomenon and Calcinosis)

The association of vasomotor disturbances with sclerodermatous changes in the skin was already well known to Raynaud (1862) and Hutchinson (1896). In 1878 Weber described a case of scleroderma with subcutaneous calcium deposits—that is, calcinosis—and in 1910 Thibierge and Weissenbach reported a case of their own and reviewed eight others from the literature in which the complete triad of scleroderma, Raynaud's phenomenon and calcinosis was present. Basch (1932) wrote a comprehensive thesis on the subject and named the condition Thibierge-Weissenbach syndrome. In view of the obscure ætiology of the condition, this eponymous and non-committal title has found wide acceptance.

According to Beerman (1948) the condition occurs almost exclusively in females, often those suffering from ovarian hypofunction, and is preceded by or associated with vasomotor disturbances, paræsthesiæ, acrocyanosis, angiospasm and Raynaud's phenomenon especially in the upper extremities resulting in sclerodactylia. In 1951 Karani reported a case to the Royal Society of Medicine under the title of " polydermatositis hæmorrhagica " ; the patient was a hypertensive male, aged sixty-one years, with scleroderma, vasomotor changes and calcinosis, and the skin biopsy showed extravasation of blood, which gave rise to the foregoing title. Coombs (1952) presented to the same society two further cases ; both patients were females, and one had œsophageal lesions. Coombs also stressed the fact that cervical sympathectomy, which is known to be of benefit in some vasomotor disturbances of the upper extremities, nearly always fails to produce any relief in the Thibierge-Weissenbach syndrome—so much so that this author states that a history of Raynaud's phenomenon persisting after sympathectomy is sometimes the earliest clue to this syndrome.

The calcium deposits in this condition are due to *calcinosis circumscripta* and limited to pressure areas such as the elbows, the ulnar border of the forearms, the finger tips, and the skin along the shin and in front of the patella and over the ischial tuberosities, in contradistinction to *calcinosis universalis*, in which calcification is much more widely distributed, affecting mesenchymal as well as subcutaneous tissue, and is usually unaccompanied by the other features of scleroderma or by Raynaud's phenomenon. The pathogenesis of calcinosis of either type, in spite of an ever-increasing volume of literature, remains obscure. Parathyroid dysfunction and disturbance of calcium metabolism have been suggested, but most authors reported normal serum calcium, blood phosphorus and blood phosphatase levels, and this was confirmed in the case reported in this paper. Calcium balance studies by Bauer *et alii* (1931) reported a tendency to retain calcium and phosphorus ; other authors, however (Goetz, 1945), reported a negative calcium balance. Histological examination of the areas of calcinosis in the present case showed the calcium to be deposited in layers running longitudinally in the direction of the laminæ of the collagen fibres. This suggests that the calcification is dystrophic rather than metastatic in origin.

The skin changes are usually, but not invariably, the first definite manifestations of the disease. In several of the cases reported in the literature, as well as in the present case, the subjective sensation of stiffness of the fingers appears before the characteristic signs of scleroderma are recognizable by the physician. The process usually starts in the hands and feet, and at a somewhat later stage the face becomes involved. The skin appears dense and tough, shiny and atrophic, and cannot be moved separately from the underlying structures. Pigmentation with occasional islets of depigmentation appears, not infrequently suggesting at first glance a diagnosis of Addison's disease. At a later stage the finger-tips taper, which makes the affected digit look like an elongated radish (Sequeira *et alii*, 1947). Small ulcers appear on the terminal part of the phalanges which in the natural course of the disease heal and then break down again. The healing and subsequent pin-point scars may occur spontaneously, and it is obviously important to be aware of that fact and not to judge the effectiveness of therapy on that criterion alone. Radiological examination of the hand will often reveal bony resorption of the terminal phalanges as exemplified in the case reported. Histological examination showed replacement of bone by rather vascular connective tissue.

Involvement of the face results in loss of skin lines and subsequent paucity of expression, reminiscent of the Parkinsonian mask-like facies. The mouth becomes more and more pinched and appears to decrease in size ; this, together with limitation of movement of the jaw, makes it scarcely possible for the tongue to be protruded and for normal mastication to take

place. This indeed may sometimes be the cause of dysphagia when no œsophageal lesions are demonstrable.

Cardio-vascular Involvement

Prior to 1943, the year in which S. Weiss *et alii* published their paper on scleroderma heart disease, little attention was paid to the cardiac manifestations of diffuse scleroderma. Matsui (1924) studied six patients, all females, every one of whom showed cardio-vascular involvement, such as cardiac hypertrophy and dilatation, mainly right-sided, and myocardial fibrosis. Heine (1926) and Brock (1934) published cases in which the cause of death was heart failure. Weiss *et alii* (1943) recorded nine cases of scleroderma and cardiac symptoms or signs ; two of these patients came to autopsy. Every one of their patients complained of exertional dyspnœa, in some instances with orthopnœa and paroxysmal nocturnal dyspnœa. Interestingly enough, in three cases these symptoms preceded the appearance, or at least recognition, of the cutaneous manifestations, and that was also the experience in the case reported in this paper. Weiss *et alii* mentioned the difficulty in the interpretation of such symptoms in view of the frequently associated pulmonary lesions and involvement of the chest wall itself. Every one of their patients was in congestive heart failure, but tricuspid incompetence was apparently not recognized. Cardiac murmurs were inconsistent, but several of their patients had a prominent diastolic gallop rhythm, and in four of the six cases, in which special attention was paid to it, the second pulmonary sound was much accentuated, which possibly indicated pulmonary hypertension. Radiological examination of the chest revealed in every instance a somewhat enlarged triangular heart shadow with limited cardiac movement. The electrocardiogram showed various abnormalities, such as conduction defects, low-voltage tracings and *ST-T* wave changes. Only one patient (Case V) showed congestive failure with auricular fibrillation, and it must be concluded that the heart in scleroderma usually fails in sinus rhythm.

Goetz (1945), who reported 13 cases of generalized scleroderma in females, stated that all his patients suffered from dyspnœa, orthopnœa and cyanosis, and one of them presented the picture of a " black cardiac ". The heart in most of these cases was small and the cardiac silhouette normal. The diagnosis of scleroderma heart was made from the kymogram, which showed obvious blunting of the cardiac excursions. Further case reports with pathological studies have been published by Mathisen and Palmer (1947), by East and Oram (1947), and at the Barnes Hospital clinico-pathological conference (1953). All these patients died of congestive heart failure ; but the morbid anatomy, except in East and Oram's case, was always complicated by pulmonary fibrosis. Recently Truelove and Whyte (1951) and Barritt and O'Brien (1952) have added case reports to the literature, but without autopsy control.

It seems apparent that several mechanisms may be responsible for the cardiac failure in diffuse scleroderma. Careful study of the published autopsy reports shows that diffuse sclerodermatous infiltration of the myocardium is very rarely the only factor in the pathogenesis, and that more often one finds right ventricular hypertrophy and dilatation secondary to interstitial fibrosis of the lungs—that is, pulmonary heart disease. Pericardial lesions appear to be common, not infrequently with effusions. An isolated instance of atypical non-bacterial verrucous endocarditis occurring with generalized scleroderma has been reported (Spuehler and Morandi, 1949) and will be referred to again.

Myocardial Lesions.—Goetz (1945) reported three different types of myocardial lesions : (i) scattered foci of fibrosis in apparently normal muscle fibres ; (ii) frank fibrosis of the entire thickness of the myocardium extending from the pericardium to the endocardium ; (iii) diffuse changes showing pronounced disintegration of the muscle fibres, which were interlaced with coarse bundles of connective tissue which was highly vascular. This last-mentioned lesion was obviously the forerunner of the second type ; all intermediate stages were observed. Goetz concluded from these observations that the myocardial fibrosis was not the result of vascular interference, especially as there were not sufficient pathological changes in the coronary arteries and no hæmosiderin pigment was found in the connective tissue. Whilst both Weiss *et alii* (1943) and Mathisen and Palmer (1947) considered that the pathological process was one of primary overgrowth of collagen fibrous tissue with secondary destruction of cardiac muscle, East and Oram expressed the opinion that the initial event was disappearance in patches of myocardial fibres with subsequent replacement by interstitial tissue, musically summarized by them in terms of Richard Strauss's tone poem " Death and Transfiguration ". With regard to the specificity of the myocardial lesions, Weiss *et alii* conclude that they are an integral part of scleroderma. The changes in the two patients whom they studied *post mortem* differed in several significant respects from other varieties

of myocardial scars. The pathological observations together with the clinical data of their cases allowed them to conclude that scleroderma heart disease was a clinical and pathological entity.

Pulmonary Hypertension.—The pathological findings in the case reported above leave little doubt that pulmonary hypertension was responsible for the cardiac failure. Already in 1924 Matsui recorded right ventricular hypertrophy and dilatation in several of his cases as a result of what he labelled " chronic productive interstitial pneumonia ", with proliferation of interalveolar connective tissue, compensatory emphysema and pulmonary vascular changes. Similar changes have been reported by Weiss *et alii* (1943), by Bevans (1945) and by Goetz (1945). McMichael (1948), in a discussion on pulmonary heart disease, mentioned scleroderma as one of the causes of the chronic form of this disease. The clinical features appear to be fairly constant in all the cases. The patient complains of increasing dyspnœa for months or years, but the progress may be so slow as to allow him or her to follow a sedentary occupation for years. The appearance of cyanosis and peripheral œdema marks the onset of the terminal stage, which rarely lasts as long as two years. Physical examination usually reveals gross limitation of chest expansion due to the pulmonary fibrosis, but also partly attributable to sclerodermatous involvement of the chest wall. Cardiac enlargement can usually be detected, but the right ventricular lift of pulmonary hypertension has not been observed or recorded, possibly owing to the fixity of the chest wall. A diastolic gallop rhythm and an accentuated pulmonary second sound are, as expected, present in the majority of cases. Increased venous pressure, enlargement of the liver and peripheral œdema, the hallmarks of right-sided heart failure, are noted in all advanced cases. Functional tricuspid incompetence with exaggerated venous systolic pulsation and pulsating liver was observed and confirmed pathologically in the present case. Although such a finding is not surprising in chronic failure of the right side of the heart, this is the first time that it has been reported in congestive failure due to scleroderma.

Radiologically, it is usually possible to recognize increased lung markings, especially in the lower zones, and enlargement of the right ventricle, the pulmonary arteries and their main branches. The electrocardiogram in the present case showed a right bundle branch block with a tall secondary *R* wave in the right ventricular surface leads — good supporting evidence of pulmonary hypertension. The present case seems to be the first one to be studied by cardiac catheterization. At the time of this investigation the patient was in untreated congestive failure, which perhaps explains the fact that the pulmonary artery pressure, although raised, does not appear as high as might be expected from inspection of the pathological material. It is also interesting to note that administration of digitalis increased the cardiac output, but did not significantly alter the right ventricular pressures.

Pericardial Lesions.—Pericardial lesions have frequently been recorded in diffuse scleroderma, even in those cases in which no other cardiovascular involvement was present. Already sixty years ago Lewin and Heller (1895) reported pericarditis in eight out of 29 cases of scleroderma, and in two of the six cases described by Matsui (1924) a pericardial effusion was found at autopsy. Pathologically the changes may vary from fibrinous pericarditis with or without effusion to chronic adhesive or fibrous pericarditis as reported by Bevans (1945) and by Sharnoff *et alii* (1951). Clinically the pericardial lesion may be suspected when a friction rub is heard, as in Case II of Weiss *et alii* (1943), or when an unusual heart shadow is discovered on fluoroscopic examination or in the X-ray film of the chest. It seems likely that in Case I of Barritt and O'Brien (1952) a pericardial effusion was present, in spite of the fact that no fluid was obtained at the two pericardial paracenteses attempted, the heart shadow greatly decreasing in size after treatment with ACTH. A similar condition was suspected in the case reported, but the position of the cardiac catheter excluded the presence of a sizable effusion.

It is perhaps not surprising that every one of the three patients of Moore and Sheehan (1952) who died of renal failure had a pericardial effusion; but Bevans (1945) concluded from her pathological studies that, in some cases at least, the lesions in the pericardium are part of the diffuse scleroderma and not merely a manifestation of the uræmic state. It may be worth while to recall that involvement of serous membranes, including the pericardium, is one of the classical features of a related collagen disease — namely, disseminated *lupus erythematosus*, a disorder which is mentioned again in the following paragraph.

Atypical Non-bacterial Verrucous Endocarditis.—In 1924 Libman and Sacks reported four cases of a previously undescribed form of valvular and mural endocarditis, two of which had obvious manifestations of disseminated *lupus erythematosus*. Subsequent studies have shown that the Libman-Sacks syndrome is

present in just half the cases of disseminated *lupus erythematosus*. It is of great interest that, although scleroderma is generally recognized as a disease of the collagen system just like disseminated *lupus erythematosus*, there is only one well-authenticated case of the presence of atypical non-bacterial verrucous endocarditis in a patient with generalized scleroderma. The patient (Case I of Spuehler and Morandi, 1949) was a man, aged forty-four years, who complained of increasing dyspnœa, joint pains and Raynaud's phenomenon. He had obvious scleroderma which was confirmed by skin biopsy, evidence of cardiac enlargement, an accentuated pulmonary second sound and a soft pulmonary systolic murmur, with a low-voltage electrocardiogram. At autopsy, in addition to diffuse scleroderma with chronic interstitial pneumonitis and fibrinous pericarditis with effusion, there were, on the auricular surface of the anterior mitral cusp, several pea-shaped craggy vegetations characteristic of the non-bacterial verrucous endocarditis of Libman and Sacks. Although the authors report a second case in the same paper, the evidence for it is not fully convincing.

TREATMENT

Many of the treatments advocated in the past for diffuse scleroderma do not stand up to critical evaluation and are therefore not worth discussion. Mathisen and Palmer (1947), for example, gave credit to a parasympathetico-mimetic drug ("Mecholyl") for the healing of digital ulcers; but it has been pointed out above that such scarring is part of the natural history of the disease. More recently improvement in skin colour, texture and elasticity was reported in four cases after multiple intravenous infusions of procaine (Turner and Schmidt, 1950). In the case reported by the Barnes Hospital clinico-pathological conference (1953), the patient was treated with 3-hydroxy-2-phenylcinchoninic acid, in accordance with the article by Blanchard *et alii* (1950), who reported its use in several cases of rheumatic fever, with some subjective and slight objective temporary improvement. The same paper mentions the use of hexamethonium in a case of generalized scleroderma, which resulted in the disappearance of the skin lesions on the chest.

The relative merits and demerits of cortisone and corticotrophin in diffuse scleroderma have been discussed since the first encouraging reports of Bayles *et alii* (1950) and of Hines *et alii* (1950), who noted in six patients amelioration of the skin lesions—with, however, return of symptoms within two or three weeks of cessation of therapy. Barritt and O'Brien (1952) reported in their Case I considerable general improvement after thirty-seven days of ACTH therapy and noted that at the time of cessation of hormone treatment the venous pressure was still raised, but returned to normal a week later. These authors concluded that it was justifiable to administer this compound in scleroderma heart disease provided that proper precautions were taken to prevent sodium and water retention.

A not so favourable impression was gained by Sharnoff *et alii* (1951), who also report on a case of diffuse scleroderma treated with cortisone. Their patient also obtained initial prompt relief and improvement, but within a few weeks pronounced hypertension with encephalopathy developed followed by rapid death in uræmia. Sharnoff *et alii* come to the conclusion that "caution and circumspection must be employed with these potent new drugs in the treatment of collagen diseases when vascular lesions are the normal occurrence". Very similarly the patient reported by the Barnes Hospital clinico-pathological conference (1953) was given 200 milligrammes of cortisone per day for the last six days of his life, during which period the blood urea level rose and the urinary output fell. On the sixth day "the patient became progressively obtunded and expired suddenly". In both these cases autopsy revealed the renal changes of scleroderma, and the conclusion seems justified that in these cases cortisone accelerates the fatal termination and is therefore contra-indicated. As in our case the cutaneous lesions were relatively unimportant compared with the gravity of the visceral manifestations, a decision against the use of cortisone or corticotrophin was made during the patient's life.

Surgical treatment in the form of cervical and upper dorsal sympathectomy has been advocated for scleroderma with Raynaud's phenomenon (Hunt, 1936; Evans *et alii*, 1953), but the results are usually disappointing (Truelove and Whyte, 1951; Cullinan, 1953)—so much so that Coombs (1952) recommends that before performing sympathectomy for Raynaud's phenomenon one should make sure that none of the other features of the Thibierge-Weissenbach syndrome are present.

SUMMARY

The case is reported of a man suffering from diffuse scleroderma, Thibierge-Weissenbach syndrome and cardiac failure due to pulmonary hypertension, studied clinically and by cardiac catheterization. The opportunity is taken to review the various ways in which the cardiovascular system may be involved. The present position with regard to treatment is briefly discussed.

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